Quantifying Uncertainty in the Efficacy of Vitamin K on Fractures in Postmenopausal Women: Economic Evaluation, Evidence Synthesis and Bayesian Meta-Analysis

by

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Institute of Health Policy Management and Evaluation
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Abstract

Vitamin K has a negligible effect on bone mineral density (BMD) and a large but uncertain effect on fractures. The three studies in the thesis explored uncertainty about the effect of vitamin K on fractures using the methods of economic evaluation and Bayesian meta-analysis.

In study 1, a Markov probabilistic microsimulation model was developed for a hypothetical cohort of 50-year-old postmenopausal women without osteoporosis. This was a fracture incidence-based model, populated with data from the literature. It was used to examine the cost-effectiveness of two supplementation strategies over a lifetime horizon. We compared vitamin K2 (or vitamin K1) concurrent with vitamin D3 and calcium versus vitamin D3 and calcium alone. Study 2 included a systematic review, and classical and Bayesian univariate meta-analyses to determine the efficacies of the K vitamins on BMD or fractures in current and future trials. Study 3 used Bayesian bivariate random-effects meta-analysis to jointly model the treatment effects on two correlated bone outcomes. We compared the estimates from the univariate and bivariate meta-analyses and explored how these results would change the conclusions of the cost-effectiveness analysis.
The strategies including vitamin K were highly cost-effective at willingness-to-pay of $50,000/QALY (quality-adjusted life year); however, the results were most sensitive to changes in the efficacy of vitamin K. The univariate meta-analyses showed large uncertainties in the anti-fracture effects of vitamin K2 in current and future trials. The bivariate 95% credible intervals were considerably narrower than those from the univariate meta-analyses. Using future odds ratios from the bivariate meta-analyses, vitamin K2 cost more than $100,000/QALY while vitamin K1 was cost-saving.

Our analyses found substantial uncertainty around the estimates of the vitamin K effect on fractures. We recommend against routine use of vitamin K for fracture prevention. Bayesian bivariate meta-analysis accounts for all available information and should be considered when the treatment effects are measured on two correlated outcomes.
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Chapter 1
Introduction

1.1 Objectives of the thesis

Osteoporosis is a highly prevalent musculoskeletal disease (1). It represents a combination of low bone mass, compromised bone strength and reduced bone quality that together lead to bone fractures (2-4). Osteoporotic fractures are associated with large personal and financial burdens (5-12); thus, their prevention is important. Vitamin D and calcium are currently recommended for the primary prevention of osteoporosis and fractures (13;14). Over the past couple of decades, vitamin K, well known for its role in blood coagulation, garnered great interest for its potential role in bone health. Studies have shown that vitamin K may be protective of fractures; however, its effect on bone mineral density (BMD) is negligible (15-20). This difference in the treatment effect on two main correlated bone outcomes has caused much controversy in the scientific community. In addition, the uncertainty about the treatment effect of vitamin K on fractures is amplified by various methodological limitations in many of the fracture-related studies with positive findings. The objectives of this thesis were to review and quantify the uncertainty in the current evidence for the efficacy of vitamin K on fractures. We used the methods of decision analysis, economic evaluation and evidence synthesis to determine the efficacy of vitamin K on fractures in current and future trials, to corroborate if there is a need for future trials and to quantify the value of future research.

In sections 1.2 to 1.4, we will review the potential roles of vitamin K in the prevention of osteoporosis and fractures, and will provide background on economic and evidence synthesis methods used to quantify uncertainties surrounding the efficacy and the cost-effectiveness of this treatment.

1.2 Background: Vitamin K and bone

1.2.1 Prevention of osteoporosis and osteoporotic fractures

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue (21). It affects one in six Canadian women aged 50...
years and older (21). A further one in two Canadian women aged over 50 are diagnosed with low bone mass or osteopenia (1). Both osteopenia and osteoporosis are detected by measuring BMD, but osteopenia is considered to precede osteoporosis (14;22;23). The main clinical consequences of osteoporosis are osteoporotic fractures – fractures that occur when low bone mass is combined with compromised bone strength and reduced bone quality (14;22;23). Osteoporotic fractures often result from injuries that would be insufficient to fracture normal bone; they are referred to as fragility fractures (1). Osteoporotic fractures occur in both women with osteoporosis and women with osteopenia (24), and the most frequent are fractures of the vertebrae, hip and wrist (25). The risk of osteoporotic fractures is high: a 50-year-old North American woman has a chance over 40% to sustain at least one in her lifetime (26).

Osteoporotic fractures also cause large personal and financial burdens: patients with fractures have decreased quality of life and increased mortality and morbidity; they also incur high healthcare costs (5-12). In Canada, the 2010 costs of acute care associated with osteoporotic fractures were estimated at $1.2 billion, while the annual costs including outpatient care, prescription drugs and indirect costs were almost twice as high (> $2.3 billion) (10). The total costs of osteoporotic fractures account for 1.3% of Canada’s health expenditures (10).

To prevent osteoporosis, non-pharmacologic treatments such as vitamin D and calcium are often recommended to postmenopausal women with osteopenia or normal BMD (13;14). Over the past couple of decades, vitamin K, well known for its role in blood coagulation, has intrigued the scientific community because of its potentially beneficial effect on bone and fractures (15-20). Vitamin K can be a promising additional primary prevention option, together with vitamin D and calcium, if its efficacy on fractures is proven. In section 1.3, we will summarize the mechanisms of action of vitamin K on bone and will review the findings of observational studies and clinical trials conducted to examine the effect of vitamin K on BMD and fractures. We will also review the safety and the costs of vitamin K.

1.3 The effect of vitamin K on bone

1.3.1 Forms and functions of vitamin K

Vitamin K represents a group of fat-soluble vitamins that exist in natural and synthetic forms (16;20). The synthetic form of vitamin K – vitamin K3 or menadione (with its derivates
vitamins K4 and K5) – is associated with toxicity, and has been banned from use for the treatment of vitamin K deficiency in North America (16;20). The two natural forms – phylloquinone or vitamin K1, and a group of menaquinones known as vitamin K2 – are essential for the human body (20;27;28). They can be found in different natural sources and have slightly different chemical structures and pharmacokinetics (29); yet, they exert the same primary effect on bone remodeling (20).

Vitamin K1 or phylloquinone represents a major form of dietary vitamin K (>90% of total vitamin K intake is from food sources) (29). The major sources of dietary vitamin K1 are green leafy vegetables (e.g., broccoli, lettuce, spinach, cabbage and kale), herbs (such as parsley, coriander and mint) and green tea (20;27;28) (Table 1.1). The primary menaquinones are menaquinone 4 (MK-4) through 10 (MK-10). MK-4 can be found in animal feeds (e.g., poultry feed and consequently poultry meat) or can be directly converted from phylloquinone in human tissues, while other menaquinones are primarily synthesized by bacteria in the gastrointestinal tract (20). Additionally, the higher menaquinones MK-7 through MK-9 can be found in legumes, fermented soy products (such as natto – a traditional food in Japan) (30;31) and fermented cheese and meats (20;27;28). MK-4 and MK-7 are available in pharmacological (pharmaceutical) forms and are the ones that have been most extensively studied in humans.

Due to lack of evidence, Recommend Daily Allowance (RDA) for vitamin K is not established in North America (32). Therefore, Dietary Reference Intake (DRI) for vitamin K is based on Adequate Intake Levels (AI) that were determined through examining hemostatic function of vitamin K (i.e., arrest and prevention of bleeding due to vitamin K deficiency). Based on the 2001 Institute of Medicine guidelines (32), the AI levels of vitamin K1 for women and men age 50 years and older are 90 mg/day and 120 mg/day, respectively (Table 1.1). The AI levels of vitamin K are determined for vitamin K1 and not for vitamin K2 due to lack of data. Also, other important functions of vitamin K beyond blood coagulation were neglected, and the currently recommended AI levels may be too low to support adequate functioning of extra-hepatic vitamin K-dependent proteins (33). Vitamin K has not been associated with any toxicity effects in animal studies so the Upper Tolerable Intake Level was not established (32).

Regarding the molecular (chemical) structure of vitamin K, all forms have a 2-methyl-1,4-napthoquinone ring, but they differ by a variable aliphatic (geranyl-geranyl) side chain at
position 3 (16;19;20). At this position, phylloquinone has a saturated phytol group, while the primary menaquinones (MK-4 through MK-10) have 4-10 repeating unsaturated isoprenyl groups (19;20). The differential chemical structure of the K vitamins most likely causes differences in their pharmacokinetics.

Table 1.1. Vitamin K1 and Vitamin K2: nomenclature, biochemical structure, adequate intake levels and potential sources

<table>
<thead>
<tr>
<th></th>
<th>Vitamin K1</th>
<th>Vitamin K2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nomenclature</strong></td>
<td>Phylloquinone, phytonadione</td>
<td>Menaquinones (MK-n)</td>
</tr>
<tr>
<td></td>
<td><strong>Primary menaquinones</strong>: MK-4-MK-10</td>
<td><strong>MK-4</strong>: Menaquinone-4, Menatetrenone</td>
</tr>
<tr>
<td></td>
<td><strong>MK-7</strong>: Menaquinone-7</td>
<td><strong>MK-7</strong>: Menaquinone-7</td>
</tr>
<tr>
<td><strong>Chemical structure</strong></td>
<td><img src="image" alt="Vitamin K1" /></td>
<td><img src="image" alt="Vitamin K2" /></td>
</tr>
<tr>
<td><strong>Adequate intake levels</strong></td>
<td>90 mg/day – females</td>
<td>Unknown</td>
</tr>
<tr>
<td>- populations age over 50 years</td>
<td>120 mg/day - males</td>
<td></td>
</tr>
<tr>
<td><strong>Food sources</strong></td>
<td>Green leafy vegetables: lettuce, spinach, cabbage and kale, brussel sprouts, broccoli</td>
<td>MK-4: animal feeds, animal tissues, converted directly from vitamin K1 in human tissues</td>
</tr>
<tr>
<td></td>
<td>Herbs</td>
<td>Other MK-n: produced by bacteria in gastrointestinal tract</td>
</tr>
<tr>
<td></td>
<td>Green tea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plant oils (e.g., olive oil, canola oil) and their products</td>
<td>MK-7-MK-9: fermented soy bean – natto, fermented cheese and meat products</td>
</tr>
</tbody>
</table>
It has been suggested that the menaquinones have greater bioavailability than vitamin K1 because of the differences in their absorption and transport (19;20). After intestinal absorption, both vitamin K1 and vitamin K2 are transported by triacylglycerol-rich lipoprotein to the liver; in the liver, vitamin K1 is metabolized and most of it is excreted (29;34). A small proportion of vitamin K1 is transported by low-density lipoprotein (LDL) from the liver to extra-hepatic tissues (29;34). Vitamin K2, or more specifically the longer-chain menaquinones, are transported by LDL from the liver to extra-hepatic tissues; MK-4 is transported to extra-hepatic tissues by both LDL and high-density lipoproteins (29;34).

Vitamin K1, MK-4 and MK-7 are available in pharmacological forms. Studies comparing the bioavailabilities and the half-lives of vitamin K1, MK-4 and MK-7 showed that MK-7 and MK-4 have greater and more stable serum levels and longer half-lives than vitamin K1 (27;29;34;35). MK-7 has a 7-8 times longer half-life than vitamin K1 (34). The menaquinones with longer half-lives, such as MK-7, appear to be the most active and the most functional forms of vitamin K (27;34;35). Compared with other primary menaquinones, the chemical structure of MK-4 is the most similar to that of vitamin K1; this is the form that exists at the highest concentrations in tissues of animals and humans (36). Studies have demonstrated that MK-4 can be converted to vitamin K1 and other K vitamins in tissues (35-37). In intestine and extra-hepatic tissues, MK-4 is indirectly formed from menadione (vitamin K3), a byproduct of the absorption of dietary vitamin K1 (35-37); also, it is directly formed from MK-7 through MK-9 during the digestion of fermented animal products (20). In the cerebrum, MK-4 is formed from dietary vitamin K1 only (35-37).

The primary function of the K vitamins is γ-carboxylation of 3-glutamic acid residue (Glu) to γ-carboxyglutamic acid (Gla). Gla enables functioning of multiple proteins present in bone and arteries referred to as vitamin K-dependent proteins (15;19;20;38-41). The active site for the carboxylation reaction is the napthoquinone ring which is common to both vitamin K1 and vitamin K2 (15). The main vitamin K-dependent bone proteins are osteocalcin, matrix Gla protein and protein S. Osteocalcin and protein S have been shown to increase bone formation, bone mineralization and bone stiffness (38;41). Osteocalcin is the most abundant bone protein produced by osteoblasts during bone formation; its ability to bind calcium is dependent on proper
\(\gamma\)-carboxylation of Glu to Gla (15;19;20). Through osteocalcin, vitamin K exerts its primary anabolic function on bone.

Another anabolic pathway has been shown for vitamin K. It has been found that vitamin K can regulate the transcription of bone-specific genes required for the expression of osteoblastic markers (42;43). In addition to the anabolic effects, vitamin K may exert some anti-resorptive effects explained through other pathways. Vitamin K may be able to affect bone turnover and suppress osteoclastogenesis through three alternative mechanisms: 1) inhibition of the nuclear factor kappa B; 2) regulation of the expression of interleukin-6 (20;44;45); and 3) inhibition of prostaglandin E2 (42;46;47).

Research has also suggested potential synergistic effects of vitamin K, vitamin D and calcium on bone that could be explained through different anabolic and anti-resorptive pathways (16). As shown in Figure 1.1, vitamin D regulates the expression of osteocalcin gene and the transcription of osteocalcin that becomes functional through the gamma-carboxilation reaction.

These anabolic and anti-resorptive actions of the K vitamins on bone, which were demonstrated in animal studies, have encouraged further investigation of potential beneficial effects of the K vitamins on BMD and fractures in humans.
Synergistic effects and common pathways: vitamin K, vitamin D and calcium

a) Anabolic pathway through gamma-carboxylation of osteocalcin (OC)

b) Anti-resorptive pathway through modulation of RANK & RANK- ligand (RANKL)

Figure 1.1.  Synergistic effects: Vitamin K, vitamin D and calcium
1.3.2 Effect of vitamin K on BMD and fractures: Observational and experimental studies

Vitamin K intake, BMD and fractures

The effects of dietary vitamin K on fractures and BMD have been examined in observational studies (Table 1.2). In total, five studies examined the effect of vitamin K intake on fractures (49;52-55). In three large prospective cohort studies that included older women and men from the USA and Norway, vitamin K1 intakes greater than 109 µg/day (48;49) and 254 µg/day (50) were associated with decreased risks of hip fractures. These studies used validated food-frequency questionnaires (FFQ) to assess vitamin K intake. However, in two other longitudinal studies, a high intake of vitamin K1 did not result in a decreased risk of hip fractures (51;52). The first study with negative findings was conducted in Denmark. It followed a population-based sample of 2000 younger women aged 43-58 years for 10 years, and it used a 4-day or a 7-day food record to assess intakes of vitamin K1 (52). Half of the study participants were on hormone replacement therapy (HRT) at baseline (52). The second study was conducted in Hong Kong. It included a convenience sample of 2944 women and men aged between 73 and 77 years whose mean intake of vitamin K1 at baseline was over 240 µg/day (51). The lack of effect of dietary vitamin K1 on fractures in these two studies might be explained by specific characteristics of the study populations which included either a large percentage of young Caucasian women on HRT (52) or older Chinese adults with high baseline intakes of vitamin K (51).

Five studies (50;52-55) examined the effect of dietary vitamin K on change in BMD. Of the three studies that included western populations (50;52;53), two were large population-based and prospective (50;52), while one included a convenience sample and was cross-sectional (53) (Table 1.2). The two large longitudinal studies (50;52) recruited samples at different risks of osteoporosis (older US adults (50) vs. younger Danish women on HRT (52)) and measured vitamin K1 intake using different methods of nutrient assessment (food record (52) vs. FFQ (50)). They found no effect of dietary vitamin K1 on BMD (50;52). A small cross-sectional study in Spanish women found a positive effect of vitamin K1 on BMD (53). Contrary to the findings of the large prospective studies in western populations, two studies in Japanese women
(one prospective and another cross-sectional) showed that a large vitamin K2 intake was associated with greater BMD (54;55).

In summary, the evidence on the effect of dietary vitamin K on fractures and BMD is limited and inconclusive.
<table>
<thead>
<tr>
<th>Author, year, country (ref)</th>
<th>Study design</th>
<th>Population Sample (N) Age</th>
<th>Vitamin K intake: Assessment Form of vitamin K</th>
<th>Outcomes</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feskanisch, 1999, USA(49)</td>
<td>Prospective cohort, Follow-up:10 years</td>
<td>Registered US nurses N= 72 327 38-63 years (mean age: 50)</td>
<td>Food-frequency questionnaire (FFQ) Dietary vitamin K1</td>
<td>Hip fractures</td>
<td>Lower risk of hip fracture in women with dietary vitamin K1 intakes &gt;= 109µg/day (age-adjusted RR: 0.70, 95% CI:0.53-0.93)</td>
</tr>
<tr>
<td>Booth, 2000, USA (50)</td>
<td>Prospective cohort, Follow-up: 7 years</td>
<td>Population-based Framingham cohort N=888 (335 men, 553 women) 68-94 years (mean age: 75)</td>
<td>FFQ Dietary and supplemental vitamin K1</td>
<td>Hip fractures</td>
<td>No associations between K1 intake and change in BMD at LS, FN, radius, trochanter, Ward’s area</td>
</tr>
<tr>
<td>Rejønmark, 2006, Denmark (52)</td>
<td>Prospective cohort and nested case-control, Follow-up:10 years</td>
<td>Population-based cohort, 50% used HRT at baseline N=2016 43-58 years (mean age:50)</td>
<td>4 and 7-day food record Dietary and supplemental vitamin K1</td>
<td>BMD (DXA)</td>
<td>Lower risk of fracture in those with the highest vitamin K1 intakes (254 µg/day) compared to those with the lowest vitamin K1 intakes (56 µg/day), RR: 0.35 (95%CI:0.13,0.94)</td>
</tr>
<tr>
<td>Apalset, 2011, Norway (48)</td>
<td>Prospective cohort - secondary data analysis, Follow-up: 10 years</td>
<td>Community-based N=2807 men and women Mean age: 72 years</td>
<td>FFQ Dietary and supplemental vitamins K1 and K2</td>
<td>Hip fractures</td>
<td>No significant differences in fracture risks between 5% of those with the lowest vitamin K intakes (&lt;25 µg/day) and 5% of those with the highest vitamin K intakes (&gt;210 µg/day), OR:0.81 (95% CI:0.24,2.73)</td>
</tr>
<tr>
<td>Chan, 2012, China (Hong-Kong) (51)</td>
<td>Prospective cohort, Follow-up: 7 years</td>
<td>Community-based, convenience sample N=2944 (1605 men, 1339 women) 73-77 years</td>
<td>FFQ Dietary and supplemental vitamin K1</td>
<td>Hip fractures</td>
<td>Vitamin K1 intake inversely associated with risk of hip fracture: for each 10 µg/day increase in vitamin K1 intake HR was 0.98 (95%CI:0.95,1.00; p=0.02)</td>
</tr>
<tr>
<td>Ikeda, 2006, Japan (55)</td>
<td>Prospective cohort, Follow-up: 3 years Analysis stratified by menopausal status</td>
<td>Population-based cohort N (total sample)=1888 20-79 years (total sample) Premenopausal women: N=788, age (mean): 34 years Postmenopausal women: N=1100, age (mean): 64 years</td>
<td>FFQ Dietary vitamin K2 from all foods and from natto (a 40g pack contains 35mg of calcium and 350 µg MK-7, suitable for 1 meal in Japan)</td>
<td>BMD (DXA)</td>
<td>In postmenopausal women, 40g-pack of natto significantly reduced bone loss at FN and the distal third of the radius: FN: -1.6±1.9% (0 natto intake) vs. -0.5±2.1% (&gt;4 weeks of natto), p&lt;0.0001 Distal third of the radius:-1.4±1.7% (0 natto intake) vs. -0.3±1.5% (&gt;4 weeks of natto), p=0.0002</td>
</tr>
<tr>
<td>Author, year, country (ref)</td>
<td>Study design</td>
<td>Population</td>
<td>Vitamin K intake: Assessment Form of vitamin K</td>
<td>Outcomes</td>
<td>Main results</td>
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<tr>
<td>Yamauchi, 2010, Japan (54)</td>
<td>Cross-sectional</td>
<td>Convenience sample of postmenopausal healthy women N=221 50-70 years (mean age: 61)</td>
<td>FFQ Dietary vitamin K</td>
<td>BMD (DXA)</td>
<td>Baseline dietary vitamin K intake: 260µg/day Negative association between the vitamin K intakes and BMD at LS (r=-0.2, p&lt;0.05) and not at FN (r=-0.1, p=0.1)</td>
</tr>
<tr>
<td>Bullo, 2011, Spain (53)</td>
<td>Cross-sectional</td>
<td>Convenience sample of postmenopausal women and men, participants of the trial N=365 55-80 years (mean age: 67)</td>
<td>FFQ Dietary vitamin K1</td>
<td>Osteoporotic fractures BMD (QUS)</td>
<td>No association between vitamin K1 intake and fractures Positive significant association between vitamin K intake and BMD (calcaneus): per 100 µg/day increase in vitamin K intake, BMD increases by 0.007 g/cm² (p=0.03)</td>
</tr>
</tbody>
</table>

RR denotes relative risk; OR denotes odds ratio; HR denotes hazard ratio; BMD denotes bone mineral density; DXA denotes Dual-Energy X-Ray Absorptiometry; FN denotes femoral neck; LS denotes lumbar spine; CI denotes confidence interval; r denotes correlation coefficient; QUS quantitative ultrasound assessment.
Efficacies of the K vitamins on BMD and fractures: Clinical trials and their meta-analyses

A number of trials in various populations have examined the efficacies of the K vitamins on BMD and fractures. Several narrative and systematic reviews and meta-analyses have summarized findings from clinical trials (15;18-20;42;56;57).

The first systematic review and classical meta-analysis was done by Cockayne et al and was published in 2006 (56). It examined the efficacy of vitamin K on BMD and fractures. The search included all published studies up to 2005 and identified 13 clinical trials for review. These trials were done in diverse populations: healthy premenopausal women, healthy postmenopausal women, postmenopausal women with primary osteoporosis, patients with secondary osteoporosis (e.g., due to biliary cirrhosis or use of glucocorticoids), and patients with stroke or Alzheimer’s disease. Two of the 13 reviewed trials were done in Caucasians and compared vitamin K1 in a dialy dose of 1 or 10 mg to control treatments; the other 11 trials were done in Japanese populations and compared vitamin K2 (MK-4) in a daily dose of 15 or 45 mg to control treatments (56). Cockayne et al found that the K vitamins increased mean BMD at the spine, hip, radius and metacarpals in all but one study (performed in premenopausal female athletes). They pooled the data of the seven trials in Japanese populations and assessed hip, vertebral and non-vertebral fractures. Their meta-analysis showed that 45mg/day of MK-4 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). However, Cockayne et al warned that these results should be interpreted with caution for many reasons. First, the vitamin K2 trials were small and fractures were detected as secondary outcomes. Second, these trials were associated with important methodological limitations such as lack of allocation concealment and lack of blinding. Next, the trials were associated with high attrition rates. The generalizability of study results was limited: Japanese patients likely had a distinct dietary pattern; also, they were older and had primary or secondary osteoporosis or prevalent fractures, and, were thus at high risk of fractures (56).
Between 2005 and 2012, several new trials examined the effects of the K vitamins on BMD. They included Caucasian populations and assessed the mean change in BMD as their primary endpoint. Interestingly, most of these trials did not demonstrate a beneficial effect of vitamin K on BMD (58-63). For example, a double-blind randomized controlled trial (RCT) in 440 Canadian postmenopausal women with osteopenia (the ECKO trial) compared vitamin K1 5mg/day to placebo for 2–4 years (60). The majority of the study population was Caucasian (88%). Supplementation with vitamin K1 did not protect against age-related decline in BMD at 2 years (60). Another double-blind RCT in 334 healthy Norwegian postmenopausal women (mean age 50) showed that 1-year supplementation with MK-7 (0.36 mg/day) had no significant effect on BMD at the lumbar spine, femoral neck and total hip (e.g., mean percent change in BMD at the lumbar spine: -0.45%, 95%CI: -0.96, 0.08) (59). Two other trials compared both preparations of vitamin K against placebo (63;64). The first 1-year double-blind RCT by Binkley et al compared vitamin K1 (1mg/day) and MK-4 (45mg/day) to placebo in a sample of 381 postmenopausal women all receiving vitamin D and calcium (63). At 12 months, the K vitamins had no effect on mean BMD at the lumbar spine or the femoral neck or on mean geometric property parameters of the proximal femur such as femur strength (63). The second open-label 1-year RCT randomized 173 Greek postmenopausal women to 4 treatment groups and compared daily supplementations with 0.1 mg MK-7 or 0.1 mg vitamin K1 both concurrently given with vitamin D and calcium to vitamin D and calcium alone or no treatment (64). Contrary to the results of the previous trial (63), the groups receiving either vitamin K1 or MK-7 had a significantly increased areal mean BMD at the lumbar spine at 12 months compared to those receiving no treatment (mean change from baseline [g/cm²]: 0.016 [K1], 0.006 [MK-7], -0.032 [control]) (64).

Since 2005, two additional trials have examined the efficacy of the K vitamins on fractures (60;65). The previously described ECKO trial by Cheung et al, which included 440 women, showed a 55% lower risk of all clinical fractures at 4 years in those receiving vitamin K1 (HR[hazard ratio]: 0.45, 95% CI: 0.20-0.98, p= 0.04) (60). This trial was of good methodological quality, but it was designed to detect a clinically significant change in its primary outcome – BMD (60). Fractures were detected as secondary outcomes, and the resulting HR estimate associated with fracture reduction had a wide 95% CI. Assuming a 10% proportion of fractures in the placebo group (personal communication with one of the authors (60)), a trial
would need 768 women per group to detect a 30% reduction of fracture risk (RR=0.7) between vitamin K and placebo (alpha=0.05 and power=0.8). The second study was an open-label phase IV clinical trial that included over 4000 Japanese postmenopausal women (65). The participants were stratified into two groups by the presence or absence of vertebral fractures at baseline, and they were randomized to MK-4 (45mg/day) plus calcium (1200mg/day) or calcium alone. It compared incidence rates of new vertebral fractures, clinical fractures and the loss of height between the two treatment groups. In both groups (those with baseline vertebral fractures [average age: 74 years] and those without vertebral fractures [average age: 67 years]), compared to calcium alone, MK-4 plus calcium did not significantly reduce the cumulative incidence of new clinical fractures (2.5% vs. 2.1%) or new vertebral fractures (5.9% vs. 5.7%) (65).

However, among the patients with at least five vertebral fractures, the incidence of new vertebral fractures was significantly lower in those receiving vitamin K2 (MK-4 plus calcium vs. calcium alone: 20.3% vs. 33.2%). Also, in patients with baseline fractures and particularly in those with at least five vertebral fractures at baseline, the decrease in height at 12 months was significantly less with vitamin K2 plus calcium than with calcium alone (in the whole sample, p value=0.059; in patients with >5 fractures, p value =0.034) (65).

Lastly, a meta-analysis published in 2011 by Fang et al compiled the data from all vitamin K trials in healthy populations, and patients with primary or secondary osteoporosis. They analyzed the changes in BMD but not the changes in incidence of fractures (57). Based on the data from all populations, Fang et al found that vitamin K use for six to 36 months increased mean BMD at the lumbar spine by 1.3% (95% CI: 0.5-2.1) (57). After excluding low-quality trials, there was no significant effect of vitamin K on BMD at the lumbar spine. The authors cautioned about likely biased estimates of the treatment effect resulting from large differences in study populations, variable methodological quality of the pooled trials and publication bias.

In summary, the current evidence based on individual trials or their meta-analyses suggests a small effect of vitamin K on BMD and a positive but largely uncertain effect on fractures.
1.3.3 Safety, costs and cost-effectiveness of the K vitamins

The K vitamins were shown to be well tolerated and safe (15;20;33;56;60;63;65). No significant increases in the incidence of all adverse events or severe adverse events were found with the K vitamins as compared to control treatments (15;20;33;56;60;63;65). In Japan and some Asian countries, vitamin K2 is used as a treatment for osteoporosis, sometimes combined with bisphosphonates (18). Three forms of vitamin K can be found as supplements: MK-4 (prepared by organic synthesis and almost exclusively used in Japan), K1 (a synthetic and the predominant form used in the rest of the world), and MK-7 (a natural form prepared by extraction of natto, a fermented soy product) (34). Vitamin K1 and vitamin K2 can be found over the counter or on the internet (34), as their costs are unregulated, but they remain unapproved for the treatment or prevention of osteoporosis in North America.

Although a number of studies have evaluated the efficacy and the safety of the K vitamins, little is known about their cost-effectiveness for the prevention of osteoporotic fractures. No study explored the lifetime cost-effectiveness of the K vitamins for the prevention of osteoporotic fractures in women initially without osteoporosis; only one economic evaluation by Stevenson et al examined the cost-effectiveness of vitamin K1 against alendronate over 10 years for fracture prevention in British women with already established osteoporosis (66;67). In the main analysis, the incremental cost-effectiveness of vitamin K1 over alendronate was associated with a favorable incremental cost-effectiveness ratio of £15,240 [$24,714]/quality adjusted life-year (QALY) gained. However, additional sensitivity analyses including value of information analyses suggested sensitivity of the cost-effectiveness ratio to the efficacy of vitamin K1; large decision uncertainty associated with high expected values of perfect information suggested the need for further investigations (66;67).

1.3.4 Clinical equipoise: Uncertainty in the efficacies of vitamin K2 and vitamin K1 on fractures

Our review of the current literature suggests three major controversies surrounding the effects of the K vitamins on bone outcomes. The first controversy results from systematic differences in the treatment effects on BMD between study populations. Vitamin K2 was protective of bone loss in elderly Japanese women (56), while vitamin K1 had no effect on BMD in postmenopausal Caucasian women (58-63). It remains unclear whether these differences between the populations
are real, possibly caused by specific environmental or genetic factors, or are spurious, possibly caused by limited methodological quality of the trials done in Japanese populations.

The second controversy relates to strikingly large reductions of fractures with both vitamin K1 and vitamin K2 shown in the majority of trials that assessed fracture as an outcome. These reductions are of similar magnitude to those of pharmacologic treatments (56). In Japanese (56) and Caucasian study populations (60), the K vitamins reduced fractures between 55% and 80%. Relatively large fracture reductions are questionable as the evidence resulting from the vitamin K studies is limited. The efficacy of vitamin K2 in Japanese populations is based on a small number of trials (56), and the efficacy of vitamin K1 in Caucasian postmenopausal women is based on a single trial (60). The confidence intervals around the mean treatment effects are wide, ranging from small to large risk reductions. In a methodological study that pooled the results of 13 meta-analyses that compared small to large trials, the treatment effects in small trials were more beneficial and were overestimated (68). There was only one large open trial in around 4000 Japanese postmenopausal women (65) that showed no effect of vitamin K2 on the incidence of fractures. It found a positive statistically significant effect of vitamin K2 only for a subgroup of patients with at least five prevalent vertebral fractures. Additionally, the methodological quality of the vitamin K2 trials is low: there is a high chance of selection and detection bias due to lack of allocation concealment, lack of blinding and high attrition. Also, the vitamin K1 trial (60) was well-designed, but fractures were detected as secondary outcomes. Therefore, evidence on the efficacy of vitamin K on fractures remains limited and inconclusive.

Lastly, most trials showed that the effects of vitamin K on two correlated bone outcomes – BMD and fractures were in opposite directions. BMD is one of the strongest predictors of fracture risk, represents a measure of bone strength and is an intermediate outcome frequently used in clinical trials (25;69;70). Therefore, it is plausible to expect that if any positive effect of vitamin K exists, it should be consistently detected in both bone outcomes. The controversy pertinent to a positive effect of vitamin K on fractures and a lack of its effect on BMD has been explained through the alternative mechanisms of actions (17;20), and its effects on bone geometry, bone strength and bone quality (17;71). Nevertheless, to date no evidence synthesis has used all available data to estimate the simultaneous effect of vitamin K on both BMD and fractures. Moreover, few studies used advanced quantitative methods to explore uncertainties surrounding the true treatment effect of vitamin K. These methods, such as cost-effectiveness analysis, value
of information analysis and Bayesian random-effects meta-analysis, can investigate uncertainties and trade-offs and their respective consequences (72-76). These methods can also help elucidate the gaps in knowledge and assist in decision- and policy-making regarding the adoption of vitamin K for the primary prevention of osteoporotic fractures in postmenopausal women.

In section 1.4, we will provide background on the methods of decision analysis, economic evaluation and evidence synthesis used to explore and quantify uncertainty.

1.4 Background: Economic evaluation and evidence synthesis as vehicles for quantitative uncertainty analysis

Statistical modeling is an essential part of quantitative research because it makes use of collected data and helps researchers draw a conclusion (77). Every statistical model includes three important parts: input variables, output variables and the nature of the relationships between these variables (77). Statistical modeling has two main goals: to explore and estimate the nature of the relationship between the input and the output variables, and to make predictions from the observed data and consequently, validate them on other empirical datasets or on simulated data (77). To achieve these goals, two different modeling methods can be used: the first relates to algorithmic modeling such as decision trees and neural nets, while the second relates to regression modeling including complex hierarchical or straightforward regression analyses (linear, logistic or Cox) (77). Since estimates derived from statistical models are always surrounded with uncertainty, a natural extension of statistical modeling could be quantitative uncertainty analysis (78-80). In sections 1.4.1 to 1.4.4, we will describe how algorithmic and regression types of modeling applied to the areas of medical decision analysis and evidence synthesis can serve to quantify and explore parameter and decision uncertainties embodied in the case of vitamin K.

1.4.1 Quantitative uncertainty analysis using decision analysis and economic evaluation

Complex or unfamiliar clinical problems and health care decisions are associated with uncertain outcomes and important trade-offs (73;75;81;82). Trade-offs may be different for the different parties involved in the decision making process (73;75). For example, for clinicians, the highest expected benefit refers to maximizing the patients’ length of life and their quality of life (83), while for policy-makers, the highest expected benefit refers to maximizing population health
outcomes through an optimal and efficient allocation of scarce and fixed healthcare resources (81;82). To calculate the highest expected value, mathematical models are used to combine all relevant data and to simplify a compound problem and present it as a set of smaller and connected parts (73;75). The concept of the highest expected value is the basis for decision science and expected utility theory and the approach of calculating it is called expected value decision-making (75;84). It is a quantitative framework that combines the tools of decision analysis and economic evaluation (e.g., cost-effectiveness analysis); it also assists decision-makers, policy-makers and clinicians in making consistent, rational and better decisions (72;73;81;85).

1.4.2 Decision-analytic models and economic evaluations

Decision-analytic models in healthcare involve statistical models of the algorithmic type (77); the input variables of these models include diverse types of data such as probabilities, rates, risks, costs and efficacies of treatments that are necessary to represent a medical problem realistically (86). The nature of their relationship can be represented by models that are used to generate single or multiple output variables such as life expectancy, quality-adjusted life-expectancy and lifetime costs (86). Decision-analytic models are vehicles for economic evaluations because they synthesize data on the costs and the benefits of alternative clinical strategies and they estimate the expected mean costs and the expected mean effects associated with each strategy; they also generate the expected incremental costs and the expected incremental benefits of one alternative over another (86).

Most types of economic evaluations take a certain perspective and compare incremental costs and incremental health effects of the clinical strategy (87). The most common types of economic analyses in health care are cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). The outcome part of the analysis differentiates CEA from CUA (87). If the increments in health effects are measured or expressed in natural units of effectiveness, such as life-years gained or numbers of fractures averted, the economic analysis is referred to as CEA, while if the increments in health effects are measured in quality-adjusted life-years (QALYs) gained, it is referred to as CUA (87).

A QALY is an economic measure that jointly accounts for the changes in quantity of life (mortality) and the changes in quality of life (morbidity) (87;88). This quality adjustment is
based on values or weights generally referred to as utilities. Utility weights are based on preferences; for example, they reflect the strength of preference or desirability of the health state, such as being alive (83;87;88). Utility weights are often anchored on the best possible health and death and are measured on an interval scale (87). The two anchors can take any pair of values conditional on the fact that one set must be smaller than the value of the other. Many economic evaluations use the conventional scale of QALY anchored at two weights: zero for death and one for the best possible health (83;87;88). The value of QALY for a certain health state is calculated from the duration of that health state and the preference weight for the health state for the same duration (assuming no discounting) (87). For example, 1 year spent in a hip fracture state with a utility weight of 0.7 equals to 0.7 QALY.

In many economic analyses, the summary statistic is the incremental cost-effectiveness ratio (ICER) that is given by the difference in mean costs ($\Delta C$) between two compared strategies divided by the difference in mean outcomes ($\Delta E$) between the compared strategies (ICER = $\frac{\Delta C}{\Delta E}$) (87). The ICER is expressed as a cost per additional unit of effect in CEA or as a cost per QALY gained in CUA. It is an analytical tool often used in resource allocation when deciding whether a new clinical strategy is cost-effective and whether it should be adopted (87). This further requires knowledge of the “threshold ICER” or “lambda” which represents the maximum price that a decision-maker or a society is willing to pay for an extra unit of effect (89). Although the value of the willingness-to-pay threshold remains controversial (89), a threshold frequently used in economic evaluations is $50,000/QALY$ (90). Depending on the ascertainment of the cost and health outcome components, economic evaluations can be done from many different perspectives, for example, from a societal or a health care payer perspective (91).

Economic modeling of osteoporosis often requires the use of Markov models that can accommodate the multifaceted disease course including recurrent events (73;91;92).

**State-transition models: Markov models**

Markov models, a type of state-transition models, are useful to represent complex clinical courses of chronic diseases that can involve time-dependent variables (e.g., recurrence of
fractures after treatment with alendronate), time to event or recurring events (e.g., repeat fractures) (92). Markov models represent important stages or events of a disease through a set of mutually exclusive and collectively exhaustive health states associated with changes in both health effects and costs (93;94). In a Markov model, a patient or a cohort of patients moves through health states over a certain time period referred to as the time horizon (93;94). In a discrete-time Markov model, the time horizon of the analysis is divided into equal increments of time, termed Markov cycles. The length of the cycle should reflect a clinically meaningful time interval pertinent to the probability of occurrence of the most important events (73). In addition to the specifics of a clinical problem, the choice of cycle length should be based on remaining life expectancy and computational efficiency (92). Shorter cycle lengths result in more precise estimates of life expectancy (92). Kuntz and Weinstein indicated that shorter cycle lengths assist in generating less biased estimates of treatment efficacy than longer cycle lengths if different types of effect measures - odds ratios, relative risks and hazard ratios – are used to model the efficacy parameter (86).

We will explain transitions using the example of a single simulated patient, recognizing that these statements apply equally to cohort models. During each cycle, in case of an event, the patient makes a transition from one health state to another with a constraint to reside in only one health state at a time (93;94). The probability of making this transition is called a transition probability (93). Depending on timing and accommodation of the events, health states are divided into transient (revisited at any time), temporary (visited only once, for one cycle) or absorbing states (i.e., termination state from which patient cannot leave – e.g. death) (86;93;94). The underlying assumption of state-transition models is that transition probabilities do not depend on history (i.e., past states or time spent in the current state beyond that in the immediate past cycle) (92). This assumption, related to absence of memory in the Markov process, is referred to as the “Markovian assumption” or the “Markovian property” (92-94). Each health state has an attached value or utility weight which reveals the preference for that health state. As an individual in a Markov model moves though various health states, the QALYs are calculated by combining values of health states (utilities) and times spent in the health states (83;86;93).

Markov models (process) are often evaluated using two methods (73;86). First, cohort simulation tracks a hypothetical cohort of patients simultaneously through the model, and second, microsimulation simulation selects a patient from the hypothetical cohort and tracks each
member through the model one at a time (73;86). In microsimulation, at the end of each cycle a random number generator is used together with the transition probabilities to determine in which state the patient will begin the next cycle (93). The outcomes (e.g., the quality-adjusted survival or costs) are recorded separately for each person according to their unique pathway starting from the initial health state until the termination state (93). As a result of this individual simulation, microsimulation inherently incorporates stochastic or probabilistic uncertainty that is also termed a “first-order Monte Carlo” simulation or individual (patient)-level simulation (79;92;95). An overall outcome (e.g., quality-adjusted survival) is calculated as the average of all individual outcomes in the sample (e.g., all individual QALYs) (93). As opposed to cohort models, microsimulation models can accommodate a large number of health states without growing the Markov state space (i.e., “state explosion”) (92). Microsimulation models are not limited by the “Markovian property” as they simulate one person at a time and track the previous events using “tracker” or counter variables; in this way the record of past events can affect future transition probabilities, that is the risk of future events conditioned on a number of the past events (73;92).

Microsimulation models seem more appropriate than cohort models to represent osteoporosis. With the use of “tracker variables”, the major events – various types of fractures - are memorized (and counted). The complexity of the disease is represented without the “state explosion” as the number of health states is greatly reduced (92); cohort models would require a large number of health states to represent the first, second and other repeat unilateral or bilateral fractures and their combinations within multiple skeletal sites. Microsimulation models also easily track individual changes in clinical history over time including the changes in the types and the numbers of the first and repeat fractures and changes over time in other important risk factors such as age.

A complex Markov model is sometimes seen as a “black box” (86), as the nature of the relationship between the input and the output data looks hidden to a non-analyst. One of the most important roles of a modeler is to investigate the “black box” and determine all sources of uncertainty that can affect the output estimates and can change the conclusions of an economic study. In the following section, we will describe the methods used to handle and present various types of uncertainty in decision models.
Investigating and presenting uncertainty in Markov models

The main purpose of economic models is to estimate expected costs and expected effects but these estimates can often be associated with substantial uncertainty (95). There are three types of uncertainty in economic evaluations: heterogeneity, variability (chance) and decision uncertainty (76;96). Decision uncertainty consists of parameter uncertainty which is internal to the model, and structural uncertainty which is external to the model; structural uncertainty is related to the assumptions used to build a model (76;96). These three types of uncertainty – heterogeneity, variability and decision uncertainty – have different repercussions on resource allocation, the costs of making wrong decisions and policy-making (73;76;79;87;95;97). For example, variability is important to clinicians and guideline developers because their recommendations are tailored towards individual patients and conditioned on patient characteristics; it is less important in economic evaluations intended to inform policy decisions that occur at a societal level (76;95;97). In contrast, decision uncertainty systematically affects adoption of a decision, causes systematic differences in the conclusions of economic analyses and is of interest to decision and policy-makers responsible for allocating resources at a societal level (76;79;95). The three types of uncertainty are also recognized in other disciplines (96). To prevent confusion, we will define the terminology as suggested in the 2012 ISPOR-SMDM modeling guidelines (96).

It is important to differentiate heterogeneity from variability (chance) (76;96). Heterogeneity is a systematic difference across patients in outcomes such as expected costs and expected effects that does not occur by chance and that can be explained by some observed patient characteristics (e.g., age, risk factors, past history) (73;76;96). In contrast, variability referred to as stochastic uncertainty or first-order uncertainty represents stochastic (random) variation in expected costs and expected effects within a homogeneous group of patients (76;97). First-order uncertainty is unknown (or unexplained): patients facing the same probabilities and the same outcomes will experience the effects of a treatment differently just due to chance (96). This type of uncertainty is also called Monte Carlo error; it is analogous to error term in statistical regression models (96). In certain types of models that include patient-level simulations (e.g., discrete-event simulations or Markov microsimulations), stochastic uncertainty needs to be eliminated in order to assess properly parameter uncertainty (96). Therefore, the 2012 ISPOR-SMDM guidelines
recommend that microsimulation models should simulate a sufficiently large number of
individuals to generate stable estimates of expected values (92).

It is also important to distinguish variability (first-order or stochastic uncertainty) from parameter
uncertainty, also referred to as second-order uncertainty (76;96). The analogous term in
statistical regression modeling is standard error of the estimate (76;96). Parameter or second-
order uncertainty is the uncertainty in estimation of the parameter of interest; it means that its
ture mean value is uncertain or unknown. Uncertainty in the mean estimate of a parameter
directly relates to the sample size used to generate the estimate and variance in the data (96).
Other causes of parameter uncertainty relate to a lack of source data or the methodological
limitations of studies used to inform estimation of the parameter (96).

In addition to different types of uncertainty, Markov models will not accurately estimate mean
effects when there are non-linear relationships between model parameters (98). A method that
can handle both parameter uncertainty and nonlinearities is probabilistic sensitivity analysis
(PSA) (76;96). In the next section, we will describe PSA and other methods used to assess
uncertainty in the ICER and used to determine the costs of making wrong decisions (76;99-104).

Handling parameter uncertainty: Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) accounts for joint uncertainty in model parameters and
expected mean values of the estimates for both linear and non-linear models (96;98). To capture
joint parameter uncertainty in a PSA, the values of input model parameters should be represented
as probability distributions rather than as constants (as in a deterministic model) (98). Different
probability distributions can be chosen using parametric (central limit theorem) or non-
parametric assumptions (76;96). For example, the beta distribution (conjugate to the binomial
distribution) can be specified for probabilities, the log-normal distributions for the measures of
relative treatment efficacy (odds ratios or relative risks) and the gamma distribution for costs or
utilities (76). For the utility parameter, the upper limit of the gamma distribution needs to be
restricted to 1 as the distribution ranges between zero and infinity (76;96). Initial uncertainty
characterized by probabilistic input variables is further propagated through the model resulting in
distributions for the model outputs including expected costs and expected effects (76;95). In
microsimulation modeling, parameters are randomly sampled from their distributions N times (e.g., N=1000) and then, they are plugged in for each of M patients (e.g., M=2000) (105). These simulations include N number of outputs or samples (i.e., 1000) and are computationally intensive; the N generated samples represent the distribution of the expected outcomes (105).

**Quantifying uncertainty in the cost-effectiveness ratio: The cost-effectiveness plane and acceptability curves**

Probabilistic models generate the distribution around incremental cost (ΔC) and incremental effect (ΔE) and the joint cost-effect distribution (76). **Figure 1.2a** shows 1000 outputs of ΔC and ΔE on the cost-effectiveness plane, generated from a second-order microsimulation on 1000 patients. ΔE and ΔC belong to a bivariate joint distribution assuming multivariate normality and the same covariance structure as the simulations (76). Given this assumption, a 95% confidence ellipse covers 95% of the estimated joint density and can be used to represent uncertainty around the ICER (76). As mentioned before, the ICER is a ratio that compares a new (vitamin K) to an old (vitamin D) strategy; it is equal to the difference in mean costs (ΔC) between the two strategies divided by the difference in mean effects (ΔE) between the strategies ( ICER= ΔC/ΔE) (76). On the cost-effectiveness plane (Fig 1.2a), the ICER of the vitamin K strategy is the slope of a straight line from the origin that passes through the (ΔE, ΔC) coordinate. If the ICER is less than the maximum amount that decision-makers are willing to pay to achieve one unit of effectiveness (e.g., a willingness-to-pay threshold of $50,000/QALY in Fig 1.2a), the vitamin K strategy should be adopted (76).

It is important to understand that the ICER and uncertainty around it, represented by the joint cost-effect density of ΔC and ΔE, must be determined within the context of the cost-effectiveness plane: in order to interpret the meaning of the ICER correctly, the analyst should know in which quadrants of the cost-effectiveness plane the ICER resides (95;106). When the joint bivariate distribution of ΔC and ΔE covers more than one quadrant of the cost-effectiveness plane, there can be two negative ICERs of the same magnitude that have the opposite meaning (106). More specifically, one negative ICER results from a negative incremental cost and a positive incremental effect (less costly, more effective) and resides in the south-east quadrant, while the second negative ICER of the same magnitude results from a positive incremental cost...
and a negative incremental effect and resides in the north-west quadrant (more costly, less effective) (Figure 1.2a) (106).

The method of cost-effectiveness acceptability curves is an alternative method to quantify and graphically present uncertainty in the ICER (107). Cost-effectiveness acceptability curve (CEAC) is an important analytical tool that allows decision-makers to examine the conclusions of an economic analysis for various willingness-to-pay thresholds (79;108). It represents the probability of incremental cost-effectiveness of the optimal strategy and is calculated from the proportion of simulated points on the cost-effectiveness plane ($\Delta C$ and $\Delta E$) that fall below and to the right (or the southeast) of a line with slope that equals to the willingness-to-pay threshold (Figure 1.2a and Figure 1.2b) (79;106;107). As shown in Figure 1.2b, a CEAC graphically outlines the probability of cost-effectiveness of the vitamin K strategy for any particular willingness-to-pay threshold on the x-y coordinate system. The x-axis represents probability that intervention is optimal (range: 0 to 1 or 0 to 100%) and the y-axis represents various willingness-to-pay thresholds (range: $0$ to $100,000$ per additional unit of effect) (108). CEAC can take many shapes, depending on the spread of the bivariate distribution of incremental costs and incremental effects in the cost-effectiveness plane (109). When the entire joint cost-effect distribution is in the north-east quadrant (i.e., the intervention is more effective and more costly), a CEAC is an increasing function of the threshold, starting at probability zero with an asymptote to 1 (109).
Figure 1.2. Joint cost-effectiveness density in the cost-effectiveness plane (1a) and the corresponding cost-effectiveness acceptability curve (1b) for the willingness-to-pay threshold of $50,000/QALY. Figure 1.2a depicts four quadrants in the cost-effectiveness plane: NE (north-east), NW (north-west), SW (south-west) and SE (south-east). The grey solid line represents the threshold ratio of $50,000/QALY. Figure 1.2b depicts the probabilities of incremental cost-effectiveness of vitamin K over vitamin D plus calcium for various willingness to pay thresholds ($/QALY).
Quantifying incorrect decision-making: Value of information analyses

By combining uncertainty in model parameters within PSA, the analyst can also use value of information analyses to address the consequence of decision uncertainty regarding the cost of opportunity lost from making the wrong decision (76;97;101). This is important because poor quality evidence may lead to the adoption of inadequate clinical strategies if the evidence is presented as truly known and fixed and not as unknown and uncertain (101). Value of information analyses quantify the value of having perfect information or the expected benefit of collecting additional information and thus, indicate sufficiency of available evidence that was used to identify the optimal decision (101). They include: the total expected value of perfect information (EVPI), the expected value of partial perfect information (EVPPI), the total expected value of sample information (EVSI) and the parameter-specific EVSI (76).

The total EVPI and the EVPPI determine an upper limit or the maximum costs that decision-makers should be willing to pay for additional research (100). The total EVPI is an extension of PSA as it examines concurrently the probability of a decision change and the costs of such change (110). The total EVPI represents the price that a decision-maker is willing to pay to remove all parameter uncertainty surrounding the strategy that has been chosen as optimal by the baseline PSA (76;101;110). It is formally calculated from the difference between the maximum expected benefit of the best decision (based on perfect information) and the expected benefit of the optimal strategy (76;101;102). The total EVPI is estimated per patient and can be calculated for a relevant population of patients (76;101). It is calculated at a priori specified willingness-to-pay thresholds (e.g., $50,000 and $100,000/QALY) (76;101). If the total EVSI is not calculated than the total EVPI could be used to examine whether further research is required. When the total EVPI exceeds the expected costs of additional research, further data collection may be both recommended and cost-effective (76;101;102). As shown in Figure 1.3a, the total population EVPI can be graphically presented over various willingness-to-pay thresholds. In the simplest case, if the total EVPI at a common willingness-to-pay threshold is very high, then additional research is worthwhile. An additional analysis – the EVPPI identifies key model parameters that contribute to decision uncertainty and drive a change of the optimal strategy (76;105;110). It is preferable to report EVPPI values for correlated groups of parameters rather
than the total EVPI (96) (**Figure 1.3b**). The parameters with the highest EVPPI might represent the focus of future research (76;96;105).

Similar to the total EVPI, which quantifies the expected costs of decision uncertainty resulting from a decision model on a hypothetical study with an infinite sample size (101), the total EVSI quantifies decision uncertainty based on empirical trial of a certain size (104). As the sample size of a trial increases towards an infinite sample, the total EVSI approaches the total EVPI; this is why the total EVPI represents the upper limit to EVSI (76). The total EVSI determines the size of expected opportunity loss due to making the wrong decision by accepting the trial’s results as true (104). To confirm whether an additional trial is needed, the total EVSI is compared against the expected total costs of a new trial and the difference is termed the expected net gain (ENG) (103;104). In the EVSI method, the expected costs of a future trial are precisely estimated by adding the financial trial costs (the costs of recruitment plus the trial costs) to the expected opportunity costs (as some patients will be allocated to placebo or less beneficial treatment) (103;104). ENG is the most valuable statistic because it identifies whether the current evidence is insufficient, and whether acquiring additional evidence through a new trial is necessary (103;104). In addition, the EVSI can be calculated for the parameters with the highest EVPPI (76). For very large samples, parameters identified by the EVSI and the EVPPI will be the same; however, this may not hold true for smaller samples. Therefore, calculations of the parameter-specific EVSI are important when estimating the sample sizes of future studies aimed to inform individual parameters (76).

In summary, uncertainty in microsimulation (patient-level) models can be characterized using the methods of PSA, acceptability curves and value of information. In the sections 1.4.3 and 1.4.4, we will describe how quantitative methods of evidence synthesis can be used for characterizing uncertainty in only one parameter – the true mean effect of a treatment.
Figure 1.3. Total expected value of perfect information (EVPI) and the expected value of partial perfect information (EVVPI). Figure A presents the values of total EVPI calculated for person ($) for various willingness-to-pay thresholds. Figure B presents total EVPI and EVVPI for the following parameters: treatment efficacy, costs and utilities.
1.4.3 Quantitative uncertainty analysis in evidence synthesis

Meta-analysis

Evidence synthesis is a methodological approach used to summarize the results of clinical trials. Meta-analysis – a quantitative component of an evidence synthesis (systematic review) – yields an overall mean for the treatment effect by combining the trial-specific estimates of the treatment effect (80;111-113). Meta-analyses are used to evaluate the state of current knowledge and identify a gap in knowledge; consequently, they can be used to inform decisions regarding future research (114-118). Based on an assumption regarding the presence of variation in the true effect between the pooled trials, meta-analytic models are divided into fixed-effects and random-effects models (80;111-113).

Fixed–effects and random-effects meta-analyses

A fixed-effects meta-analysis assumes homogeneity of the combined trials and allows for variability in the effect estimates due to sampling error alone (111-113). Thus, in a fixed-effects model, although the combined trials result in various estimated treatment effects denoted as $Y_i$ with different within-study variances denoted as $\sigma_i^2$, the true treatment effect is assumed equal for all trials (111-113). The common treatment effect is denoted as $\theta$ (111-113):

$$Y_i \sim N \left( \theta, \sigma_i^2 \right) \quad \text{for } i = 1,2 \ldots k \text{ independent trials} \quad (1)$$

The most common approach to obtaining a pooled fixed-effects estimate of a treatment effect is called the generic inverse variance approach. In this approach, the treatment effect estimated for trial $i$ is given a weight denoted as $\omega_i$, inversely proportional to the within-study variance. This is termed as an inverse-variance weight $\omega_i$, which in a fixed-effects model, is calculated as (111-113):

$$\omega_i = \frac{1}{\sigma_i^2} \quad \text{for } i = 1,2 \ldots k \text{ independent trials} \quad (2)$$
Using the inverse-variance weighting method, the pooled estimate, denoted as $\bar{Y}$ (i.e., the estimate of $\theta$) is calculated as weighted average of all observed treatment effects (111-113):

$$\bar{Y} = \frac{\sum_{i=1}^{k} \omega_i Y_i}{\sum_{i=1}^{k} \omega_i} \quad \text{for } i = 1,2 \ldots k \text{ independent trials} \quad (3)$$

It is more realistic that the true treatment effects differ across the combined trials, due to various reasons (e.g., differences in study populations, exposures, outcomes or methodological quality) (80;111-113;119). In these situations, a random-effects meta-analysis is more applicable because it accounts for both random within-study sampling error and between-study heterogeneity (80;111-113). Random-effects models assume that observed treatment effects (denoted as $Y_i$ for each trial $i$) are sampled from their corresponding but different normal distributions, each study having a different underlying true mean $\theta_i$ and within-study variance $\sigma_i^2$ (80;111-113):

$$Y_i \sim N(\theta_i, \sigma_i^2) \quad \text{for } i = 1,2 \ldots k \text{ independent trials} \quad (4)$$

In a random-effects model, this population of true study-specific treatment effects, denoted as $\theta_i$, belong to the same normal distribution governed by some mean and variance (80;111-113):

$$\theta_i \sim N(\mu, \tau^2) \quad \text{(5)}$$

The mean $\mu$ represents the mean of the study-specific effects and the variance $\tau^2$ represents their between-study heterogeneity. Thus, a random-effects model is a hierarchical model with two defined levels as illustrated by equations 4 and 5. Under the random-effects model and as per the inverse-variance weighting method, the weight given to each trial denoted as $\omega_i$ includes both types of variability (80;111-113):

$$\omega_i = \frac{1}{\sigma_i^2 + \tau^2} \quad \text{for } i = 1,2 \ldots k \text{ independent trials} \quad (6)$$

The weighted population mean $M$ (i.e., the estimate of $\mu$) is computed as the following weighted average of effect measures (80;111-113):
\[ M = \frac{\sum_i^{k} \omega_i Y_i}{\sum_i^{k} \omega_i} \] (7)

Meta-analyses of single and multiple outcomes

Although most treatments have effects that are measured on various outcomes (120-123), most meta-analyses are conducted as univariate analyses separately pooling effect sizes measured on each outcome (123;124). When within one study, the effect of treatment is examined on several different outcomes or across several comparison groups or several time points, then the treatment estimates on multiple outcomes (comparison groups or time points) are correlated (120;125). Consequently, in conducting separate univariate meta-analyses, information is lost, the dependence between the treatment estimates is ignored, a risk of Type I error or a false positive result is increased and the estimates of the pooled treatment effect are potentially biased (125).

Multivariate meta-analysis is a joint synthesis of the treatment effects measured on multiple outcomes that uses all available data and takes into account correlations (122;126-132). The simplest and the most frequently used type is bivariate meta-analysis that simultaneously analyzes a treatment effect measured on a pair of outcomes (127;129;132;133). Bivariate meta-analysis estimates the population mean treatment effect for each outcome and the correlation of these effects across studies (127;134). The between-study correlation indicates whether the direction of the changes tends to be in the same or the opposite direction.

As indicated by Higgins et al, univariate or multivariate random-effects meta-analyses have two important roles: first, to summarize the current knowledge, and second, to make a prediction of a treatment effect in a future trial (80). By predicting future treatment effects, random-effects meta-analyses can identify whether a future study is required or the current knowledge is sufficient. The prediction intervals of treatment effects in future studies can be estimated by previously described classical or frequentist methods of random-effects meta-analysis (119). However, the Bayesian approach to random-effects meta-analysis represents a natural setting for predicting the treatment effect in a future study because it accounts for all uncertainty in the true treatment effect by treating model parameters as probabilistic (115;135).
Bayesian random-effects meta-analysis

Bayesian models combine existing with prior information to produce updated knowledge (115). In Bayesian terms, existing observed data or current evidence about a parameter of interest is summarized by the likelihood; prior information relates to beliefs or opinions about the parameter (e.g., efficacy of a treatment) that may or may not be evidence-based; the new knowledge is produced by updating priors with current evidence and is referred to as a posterior (115). These key elements – prior, likelihood and posterior – are represented by probability distributions. While classical methods model parameters as fixed but unknown (80), Bayesian random-effects meta-analysis allows better characterization of parameter uncertainty through explicit probabilistic modeling of all model parameters. In the following section, we will outline important differences between classical and Bayesian random-effects meta-analyses.

Classical random-effects models acknowledge differences between the trials’ true treatment effects and assume that they are randomly sampled from a population of studies (80;111-113). Compared to classical models, Bayesian random-effects models relax or expand this assumption: they express uncertainty or lack of knowledge regarding differences in the true treatment effects through the assumption of exchangeability (115). Exchangeability of the trials’ treatment effects means that although the different treatment effects are sampled from the same distribution, a priori there is no reason to believe that a treatment effect of one trial is larger than the treatment effect of any other trial (115). In Bayesian random-effects models, the analyst acknowledges differences in trials’ effect sizes (denoted as $\theta_i$ in equations 4 and 5) without making any prediction of the rankings of their magnitudes or without considering any explanation about what caused this variability (135). Similar to classical meta-analysis, Bayesian random-effects meta-analysis has a hierarchical structure (as shown in equations 4 and 5); but, it involves an additional complexity, because the lack of knowledge regarding the heterogeneity of the effect sizes is specified through prior distributions, allowing for uncertainty in estimation of between-study variance (115;135). Next, in Bayesian meta-analyses, when all treatment effects are combined, the model updates the estimates of the individual trials accounting for the results from all the other studies (115;136). This process, referred to as “borrowing strength”, causes shrinking of confidence intervals for each individual trial (compared with the width of the interval obtained by classical meta-analysis); it also moves the point estimates towards the
pooled mean (115;136). The amount of shrinkage that occurs due to “borrowing strength”
depends on the size of the within-study variances (115;136).

Although Bayesian random-effects meta-analysis is mostly used to compute the posterior
distribution of the population treatment effect in a collection of completed studies, it can be
easily extended to predict the treatment effect in a future study (80). Predictive posterior
distributions incorporate all uncertainty of model parameters; they account for the uncertainty in
the population mean treatment effect and for the uncertainty in the estimate of between-study
variance (80;119). Spiegelhalter et al (115) and Ades et al (118) propose the use of a predictive
posterior of the true treatment effect instead of the random-effects mean in decision analytic
models to ensure inclusion of all variation around the true treatment effect. Predictions of
Bayesian meta-analysis can find applications in the areas of sample size calculations (115),
decision modeling (e.g., for better estimation of parameter uncertainty in PSA)
(115;118;135;137) and value of information analyses (101;104;135;137).

However, a recognized disadvantage of Bayesian random-effects meta-analysis is related to
specifying prior distributions (115;135). In Bayesian meta-analyses, prior distributions are
assigned to parameters – the true mean treatment effect and the between-study variance denoted
as $\mu$ and $\tau^2$ in equation 5 (135;138). Often, the analyst is required to specify priors on both
parameters. It has been shown that changing distributional assumptions around the prior on the
mean treatment effect using non-informative, skeptical informative or optimistic informative
priors can substantially influence the posterior distributions of population and future treatment
effects (138;139). Previous research has suggested that appropriate modeling of between-study
variance is similarly important (80). Non-informative (vague) priors on this parameter were
considered more objective as they let the “data to dominate” (140); consequently, they have been
suggested for modeling the between-study variance (138). Lambert et al performed a simulation
study including 13 vague priors on between-study variance and demonstrated that assuming
different vague priors for between-study variance resulted in different posterior estimates of the
mean treatment effect and the between-study standard deviation (141). In addition, our empirical
study compared 10 non-informative priors on between-study variance and showed that the choice
of this prior considerably influences the predictive distribution of the true treatment effect in a
future trial (142). Therefore, sensitivity analysis is recommended to examine how various priors
on the mean treatment effect and between-study variance can alter the study estimates (115;135;141-143).

1.4.4 Investigating and presenting parameter uncertainty in Bayesian random-effects meta-analysis

Uncertainty surrounding the true treatment effect: Credible intervals, probabilities of benefits and predictive distributions

Bayesian hierarchical random-effects models combine uncertainties in all parameters through Gibbs sampling or a Markov chain Monte Carlo (MCMC) simulation to generate the posterior distributions for the population treatment effect (current studies) and between-study variance (115;143). Uncertainties in the true mean values of these parameters are presented by credible intervals (115). A credible interval (CrI) is generated from samples from a posterior distribution of the parameter of interest (115): for example, a 95% CrI for a population mean is obtained as the 2.5th and 97.5th percentiles of the samples from the posterior distribution of the population mean. A 95% CrI represents a probability statement; it indicates that the population mean lies in the range with a probability of 0.95 (115). A 95% confidence interval (CI), which is generated in classical meta-analysis, does not have this property: it indicates that in 95% of hypothetical repetitions of the study in question, the interval generated will contain the true parameter value.

Of note, the probability that the true value of the parameter is within the observed interval is either zero or one.

Bayesian random-effects meta-analysis can be used to generate other direct probability statements from the posterior distributions: for example, the analyst can calculate a probability whether the parameter exceeds 0 or a certain value of the effect size that reflects a probability of any benefit of the treatment (e.g., OR<1) (115;135;143). Computations of the probabilities of benefit can be done for both current treatment effects and predictions. A probability of the treatment benefit may be more valuable information for clinicians than statistical significance of the treatment efficacy (as defined by p values) (144;145). Clinicians often incorrectly comprehend p values with posterior inferences; they incorrectly assume p values less than 0.05 mean that the posterior odds are greater than 1 that the null hypothesis is false (145). In Bayesian hypothesis testing, given the priors and the likelihood (observed data), the analyst can
calculate the probabilities of null and alternative hypotheses being true. The hypothesis that has the higher probability is favored (115). The ratio of odds can be further used to show how many times the alternative hypothesis is as likely as the null hypothesis. Most liberally, the analyst can interpret this ratio so that posterior odds greater than 1 indicate that there is an effect of treatment; this equates to a posterior probability greater than 50% that there is a treatment effect (145). Therefore, the probability of benefit over 50% can be the least conservative threshold used to make inferences on the existence of treatment effect (135;145).

As previously mentioned, Bayesian univariate random-effects meta-analysis is used to generate an exact predictive distribution of the treatment effect in a future study for a single outcome (80). Bayesian bivariate random-effects meta-analysis may have additional advantages over the Bayesian univariate meta-analysis. In Bayesian bivariate meta-analysis, the future treatment effect is generated for a pair of correlated outcomes. Since Bayesian bivariate meta-analysis utilizes all available data and accounts for correlations, the posterior distributions of the mean effect in current or future studies are more precisely estimated (122;126;127;129;131;134). Also, Bayesian bivariate meta-analysis can meaningfully contribute to the investigation of parameter uncertainty through direct probability statements. As opposed to the univariate meta-analysis, Bayesian bivariate meta-analysis provides the probability of the treatment benefit on both outcomes.

**Uncertainty due to heterogeneity: Meta-regression and subgroup analysis**

Although random-effects models incorporate between-study heterogeneity, they do not explain the reasons for it (143). Meta-regression models can be used to explore and explain the reasons for heterogeneity through the inclusion of covariates (135). Subgroup analyses are a specific type of meta-regression that explores the effect of discrete or categorical variables (135). These analyses can show that treatment effects vary systematically or that associations exist between treatment effects and covariates (135). Covariates can consider patient or between-study characteristics such as the probability of an event in the control group or baseline risk (76;135;143;146;147). It is important to examine the relationship between baseline risk and treatment effect as the severity of disease often interacts with the efficacy of treatment (76;135;143;146;147). A regression model including baseline risk may delineate which patients
can benefit most from the treatment (135). A Bayesian random-effects meta-regression is an extension of previous models (equations 4 and 5) and can be fitted using the following generic hierarchical model (135;148):

\[ Y_i \sim N (\theta_i + \beta x_i, \sigma_i^2) \quad \text{for } i = 1,2 \ldots k \text{ independent trials} \quad (8) \]

\[ \theta_i \sim N (\mu, \tau^2) \]

where \( \beta \) is the regression coefficient related to the effect of the covariate on the treatment effect, \( \theta_i \) is a trial-specific treatment effect adjusted for the covariate effect and \( \mu \) denotes the main output or the covariate-adjusted population mean (135). In this Bayesian model, priors have to be specified on three parameters: \( \mu \), \( \tau^2 \) and \( \beta \) (135).

Meta-regression models are used to adjust for systematic differences between the trials, but they are associated with three important limitations (135;143;146;147;149). First, as with any regression model, power is limited by the number of pooled trials. Next, meta-regression models that do not appropriately model baseline risks can lead to biased estimates of treatment effect because the measure of baseline risk constitutes the part of the effect size associated with the treatment effect (135;143;147). This structural dependence between the covariate and the outcome needs to be captured in meta-regression to obtain an unbiased effect of baseline risk on the treatment effect (135;149). Lastly, meta-regression analyses are susceptible to ecological fallacy (aggregation bias) as finding a significant relationship between the covariate means and mean treatment effects may not reflect what truly occurs at individual levels (143).

1.4.5 Uncertainty due to publication bias and outcome reporting bias

Uncertainty in the true treatment effect is also related to publication and outcome reporting bias. Publication bias indicates that studies with significant or striking results are more likely to be published and thus, included in an evidence synthesis and a meta-analysis (150;151). Several methods have been suggested to detect publication bias. The funnel plot is one of the simplest methods: it graphically presents the estimate of trial-specific treatment effects against their precision (111). In the absence of bias, this scatter plot has a “funnel shape” with the effects of smaller trials spread widely around the mean effect (111) (Figure 1.4). The asymmetry of a funnel plot is often tested by Egger’s linear regression that models the standardized effect sizes
against the trials’ precision (111;113;152). Publication bias is detected if the intercept of the regression line is significantly different from zero (111;113;152). Another method that evaluates the effect of publication bias is the trim and fill method; it allows imputations of treatment effects from missing trials and recalculation of the overall treatment effect (111;113;152).

Outcome reporting bias is a type of dissemination bias related to selective reporting of the results on some but not on all measured outcomes in published studies (151). Some authors have recently proposed the method of multivariate meta-analysis to address the effect of outcome reporting bias on parameter uncertainty (153).
Figure 1.4. **Investigation of publication bias and small study effect: funnel plot and Galbraith plot.** The funnel plot is presented on the left and the Galbraith plot is presented on the right part of Figure 1.4. The test for funnel plot asymmetry using linear regression method (the Egger’s test) suggests the absence of publication bias (p value = 0.89). Galbraith plot represents a linear regression test of standardized treatment effect versus precision. It shows a negative but statistically not significant intercept of -0.11 (p value = 0.89); it suggests the absence of a small study effect and publication bias.
1.5 Rationale and overview of the thesis

Current research suggests several mechanisms through which vitamin K can positively affect bone outcomes (15;17;19;20). However, many controversies around the treatment benefit of vitamin K, caused by the methodological limitations of the vitamin K trials and lack of advanced quantitative analyses of uncertainty in the true treatment effect of vitamin K, have hindered further investigations. The scientific community is divided between those who “believe” in a beneficial effect of vitamin K and those who “reject” it as spurious.

There is large parameter uncertainty in the true treatment effect of the K vitamins that is driven by: 1) systematic differences in vitamin K effects on BMD between study populations; 2) likely overestimated anti-fracture effects of the K vitamins; and, 3) unclear directions of the treatment effects on BMD and fractures. To date no study has utilized all available BMD and fracture data to jointly model the treatment effects of the K vitamins. Additionally, there is large decision uncertainty regarding the adoption of the K vitamins for primary fracture prevention in postmenopausal women: no modeling study has determined the cost-effectiveness of the K vitamins in women initially without osteoporosis, examined uncertainty surrounding the cost-effectiveness estimates or determined the opportunity loss (the EVPI).

Consequently, this thesis research is aimed at delineating parameter and decision uncertainty surrounding the effectiveness and cost-effectiveness of vitamin K for the prevention of fractures in postmenopausal women. It will address whether there is enough good quality evidence to recommend the use of vitamin K, or whether the knowledge gap is persistent. More specifically, the three thesis studies seek to investigate the following research questions:

**Study 1:** Is lifetime supplementation with vitamin K, vitamin D3 and calcium for the prevention of fractures in postmenopausal women initially without osteoporosis cost-effective at commonly used thresholds compared to lifetime supplementation with vitamin D3 and calcium alone? Can we recommend adoption of vitamin K into clinical practice?
Study 2: Do the K vitamins protect against bone loss and fractures? What are the probabilities of showing beneficial effects of the K vitamins on BMD or on fractures? What are the predictions of the vitamin K treatment effects in future studies?

Study 3: Do vitamin K2 and vitamin K1 affect bone loss and protect against fractures in current and future studies when the changes in BMD and fracture outcomes are simultaneously modeled in Bayesian bivariate random-effects meta-analysis? If the jointly modeled treatment effects are used to populate the vitamin K economic model (from study 1), does the decision of whether to adopt vitamin K into routine clinical practice change? Based on these results, can we recommend concurrent supplementation with vitamin K, vitamin D3 and calcium for the prevention of osteoporotic fractures in postmenopausal women initially without osteoporosis?

The overall structure of this dissertation takes the form of five chapters, including this introductory chapter. The thesis presents the results of these three studies in the form of three separate papers corresponding to Chapters 2-4. The final chapter briefly summarizes the findings of the three studies, discusses their clinical and methodological contributions and their limitations. It provides an in-depth discussion of several key areas for future research.

1.5.1 Relevance of the thesis

Osteoporosis and osteoporotic fractures are major health problems in postmenopausal women. Vitamin K has been suggested as an effective and affordable option for the prevention of fractures. However, uncertainties in its clinical effectiveness and cost-effectiveness are substantial. This doctoral dissertation will use the advanced methods of decision analysis, economic evaluation and Bayesian evidence synthesis to explore these uncertainties, and will determine whether there is enough evidence to recommend vitamin K for the prevention of osteoporotic fractures in postmenopausal women initially without osteoporosis.
Chapter 2

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

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2. Study 1

2.1 Abstract

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 D3 (800 IU/day) with calcium (1200 mg/day), and vitamin K2 (45 mg/day) with vitamin D3 and calcium (at the same doses). An additional analysis explored replacing vitamin K2 with vitamin K1 (5 mg/day).

Results: Adding vitamin K2 to vitamin D3 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 K1 to vitamin D3 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 D3 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

2.2 Introduction

Vitamin K, as menaquinones (K2) or as phylloquinone (K1), 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 K2 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) (56). 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 (56). 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 K1 supplementation was found to reduce clinical fractures after 4 years (hazard ratio[HR]=0.45, 95% CI:0.20 to 0.98) (60). Although this trial was of good methodological quality, it was not designed to detect fractures as fractures were secondary endpoints (60). In addition, several trials in predominantly Caucasian populations did not demonstrate an effect of vitamins K on bone mineral density (BMD) (58-63). 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 (57). 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 (58-63) 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 (76;101;103). Thus, we evaluated the cost-effectiveness of lifetime supplementation with vitamin K for fracture prevention in postmenopausal women without osteoporosis using computer-modeling techniques.

2.3 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 3 strategies: 1) no supplementation; 2) vitamin D3 (800 IU/day) with calcium (1200 mg/day); and, 3) vitamin K2 (45 mg/day) concurrent with vitamin D3 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 K2 with vitamin K1 (5 mg/day). Finally, we performed an analysis examining the use of vitamin K2 (45 mg/day) as a single agent. Costs and benefits were discounted at an annual rate of 3% (154).

Complete details regarding methods are presented in the Appendix. Our study was approved by the Research Ethics Boards of University Health Network and the University of Toronto.

2.3.1 Model structure

The model simulated the clinical course of osteoporosis in each of 1000 hypothetical healthy 50-year-old postmenopausal women without osteoporosis or previous fractures (Figure 2.1). 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 (155;156). We assumed that morphometric vertebral fractures
were clinically unrecognized (157) 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 (14;158;159). The model was constructed using TreeAge Pro (TreeAge Software Inc., Williamstown, MA, 2009).
The figure depicts an individual-level Markov state-transition model that includes 6 health states, each represented by an oval. The simulation starts with a healthy 50-year-old postmenopausal woman without a fracture. At each one-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.

Figure 2.1. Model schematic. The figure depicts an individual-level Markov state-transition model that includes 6 health states, each represented by an oval. The simulation starts with a healthy 50-year-old postmenopausal woman without a fracture. At each one-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.
2.3.2 Fractures and mortality

We modeled fracture risks as increasing with age and with each prior fracture (Table 2.1). We assumed that each woman could sustain a lifetime maximum of 2 hip, 4 clinical vertebral, 8 morphometric vertebral and 2 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 (157;160). We assumed that fracture rates were similar between Sweden, the USA and Canada (155). We modeled the risks of successive fractures using data from a meta-analysis (161) 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 (162).

Age-specific background mortality was estimated from Canadian life tables (163). The model incorporated an increased risk of death for 12 months after a hip fracture (Table 2.1) (5) but we assumed that there was no excess mortality associated with clinical vertebral fractures (164).

2.3.3 Treatment effects

We modeled the effect of treatments as a relative reduction in fracture hazard rates (Table 2.1). The efficacy of vitamin D3 (400-800 IU/day) with calcium (1000 mg/day) was based on a meta-analysis of three randomized-controlled trials (Table 2.1). Estimates of hip and wrist fracture risk reductions were obtained from studies on populations without prior fractures (165-167), while the estimates of vertebral fracture reduction were from trials that combined populations with and without prior fractures (166;167).
The efficacy of vitamin K2 (45 mg/day) in reducing hip and clinical vertebral fractures was estimated from a meta-analysis (56) using data of 442 Japanese elderly women with osteoporosis (168-171), but excluding those with stroke, Parkinson’s or Alzheimer’s disease (172-174). We estimated the wrist fracture reduction from a single study in 241 female Japanese patients with osteoporosis (168). Fracture reductions with vitamin K1 (5 mg/day) were calculated from a single RCT trial in 440 postmenopausal Canadian women (60).

We modeled the efficacy of alendronate using estimates from a meta-analysis in women with severe osteoporosis, osteoporosis or osteopenia (175). We assumed that the relative hazard declined linearly over time after stopping the drug until there was no residual effect after 5 years (176;177).

2.3.4 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 2.1). 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 (175;178-180). In contrast, we assumed that wrist fractures affected quality of life for the first post-fracture year only (175;178-180). The utility of the no-fracture state was taken from a general Swedish population (181) (Table 2.1). For women with multiple fractures, the utility weights for each sustained fracture were multiplied together.

2.3.5 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 (11) (Table 2.1). 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 other) and long-term care costs (nursing home care, disability and dependency care) (11). 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 is no published data on the cost of multiple fractures,
we varied the fracture costs from 25-75% 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 (158) and a dispensing cost of $26 per year (182) (Table 2.1). The yearly cost of vitamin D3 (800 IU/d) with calcium (1200 mg/d) was estimated at $89.9 (158); no dispensing costs were assumed as vitamin D and calcium are available over-the-counter. We used internet sources to estimate costs of vitamins K2 and K1 including their within-US shipping cost (183-185) (Appendix). Retail daily costs for vitamin K2 (45 mg/d) varied from $1.7 to $9.9 (Appendix). We assumed a daily cost of vitamin K2 of $2.07 (as compared to the daily costs of vitamin K1 and vitamin D with calcium), yielding an annual cost of $865.2 (185). The annual cost of vitamin K1 was estimated to be $199.8 (183). All costs were adjusted for inflation and expressed in 2009 US dollars using the medical component of the Consumer Price Index (186).
### Table 2.1. Input parameters: Risks, costs and utilities

<table>
<thead>
<tr>
<th>Model Parameters</th>
<th>Base Case Values (95% CI/SE)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RISKS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsequent fracture following</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>2.40 (1.90-3.20)</td>
<td>(161)</td>
</tr>
<tr>
<td>vertebral clinical/morphometric fracture</td>
<td>2.00 (1.70-2.40)</td>
<td>(161)</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>1.90 (1.70-2.30)</td>
<td>(161)</td>
</tr>
<tr>
<td>Death, 1st year following a hip fracture</td>
<td>1.37 (1.10-1.50)</td>
<td>(5)</td>
</tr>
<tr>
<td>Fracture risk with alendronate (70 mg/week)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.62 (0.40-0.98)</td>
<td>(175)</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.56 (0.46-0.68)</td>
<td>(175)</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.64 (0.30-1.35)</td>
<td>(175)</td>
</tr>
<tr>
<td>Fracture risk with vitamin D3 plus calcium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.68 (0.50-0.92)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.87 (0.65-1.14)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.69 (0.18-2.54)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Fracture risk with vitamin K2 (45 mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.30 (0.05-1.74)</td>
<td>(56)*</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.40 (0.25-0.65)</td>
<td>(56)*</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.54 (0.20-0.85)</td>
<td>(168;175)</td>
</tr>
<tr>
<td>Fracture risk with vitamin K1 (5 mg/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.34 (0.01-8.42)</td>
<td>ECKO, (60)</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.45 (0.14-1.47)</td>
<td>ECKO</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.33 (0.09-1.25)</td>
<td>ECKO</td>
</tr>
<tr>
<td><strong>UTILITIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture, first year</td>
<td>0.890 (0.043)</td>
<td>(178)</td>
</tr>
<tr>
<td>Hip fracture, subsequent years</td>
<td>0.925 (0.048)</td>
<td>(175)</td>
</tr>
<tr>
<td>Clinical vertebral fracture, first year</td>
<td>0.900 (0.031)</td>
<td>(178)</td>
</tr>
<tr>
<td>Clinical vertebral fracture, subsequent years</td>
<td>0.930 (0.008)</td>
<td>(175)</td>
</tr>
<tr>
<td>Wrist fracture, first year</td>
<td>0.980 (0.005)</td>
<td>(175)</td>
</tr>
<tr>
<td>No fracture, age 50</td>
<td>0.985 (0.010)</td>
<td>(181)</td>
</tr>
<tr>
<td><strong>COSTS (USD)</strong> b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture, first year</td>
<td>51139.20</td>
<td>(11)</td>
</tr>
<tr>
<td>Hip fracture, 2-5 years</td>
<td>3639.90</td>
<td>(11)</td>
</tr>
<tr>
<td>Clinical vertebral fracture, first year</td>
<td>1659.40</td>
<td>(11)</td>
</tr>
<tr>
<td>Clinical vertebral fracture, 2-5 years</td>
<td>371.90</td>
<td>(11)</td>
</tr>
<tr>
<td>Wrist fracture</td>
<td>1030.30</td>
<td>(11)</td>
</tr>
<tr>
<td>Alendronate, 70 mg/week (generic)</td>
<td>131.04</td>
<td>(158)</td>
</tr>
<tr>
<td>Vitamin K2, 45 mg/day</td>
<td>865.20</td>
<td>(185)</td>
</tr>
<tr>
<td>Vitamin K1, 5 mg/day</td>
<td>199.80</td>
<td>(183)</td>
</tr>
<tr>
<td>Vitamin D3 with calcium, 800 IU + 1200 mg/day</td>
<td>89.90</td>
<td>(158)</td>
</tr>
</tbody>
</table>

*Subgroup analysis excluding the Sato studies (172-174); ECKO = the ECKO trial (Evaluation of the Clinical use of vitamin K supplementation in postmenopausal women with Osteopenia)(60); SE= standard error; b Adjusted for inflation using the US 2009 Consumer Price Index (medical component).
2.3.6 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 (157;160). We considered our model to be well calibrated because its 10-year fracture probabilities were within a 2% range of observational data.

2.3.7 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 (187). We used a willingness-to-pay threshold of $50,000/QALY gained (90) 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 (188). A strategy could also be eliminated by extended dominance if its costs and benefits are improved by a mixed strategy of two other alternatives (188).

2.3.8 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) (189;190); 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 50-100%[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 two years.
We used probabilistic sensitivity analysis to calculate incremental cost-effectiveness ratios. We specified distributions for input parameters and repeatedly sampled from those distributions (76). 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 1000 trials, each of which included 1000 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/QALY-$100,000/QALY) (187). 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 (76;101). 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 (191).

2.4 Results

2.4.1 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: Figure A2.1). Epidemiological data indicated rates of 1.1%, 11.8%, 1.9%, and 5.1%, respectively (157;160). 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:...
2.4.2 Survival gains and cost-effectiveness

Vitamin K2

Compared to no supplementation, vitamin D with calcium increased survival by 1.1 years. Addition of vitamin K2 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 2.2). Addition of vitamin K2 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 2.2). 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, addition of vitamin K2 increased discounted lifetime costs by $8,956, yielding an incremental cost-effectiveness ratio of $12,268/QALY (Table 2.2).

In 990 of 1000 simulations, vitamin K2 was associated with better clinical outcomes than vitamin D with calcium (Figure 2.2a). Vitamin K2 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 (Figure 2.2a). The probability of cost-effectiveness of lifetime supplementation with vitamin K2, 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 (Figure 2.3a). Based on a US prevalence of 26 million women with low bone mass (191), we estimated the budget impact of adding vitamin K2 supplementation to be $232.9 billion. The maximum expected population cost of additional research or EVPI for vitamin K2 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: Figure A2.5).

In a separate analysis, vitamin K2 as a single agent was associated with higher expected costs and lower expected benefits and was strongly dominated by vitamin K2 with vitamin D and calcium (Table 2.2). Compared to vitamin D with calcium alone, addition of vitamin K2 yielded an incremental cost-effectiveness ratio of $12,896/QALY. The probability of lifetime supplementation with vitamin K2, vitamin D and calcium being cost-effective at a $50,000/QALY threshold was 82.4%.

**Vitamin K1**

Compared to vitamin D with calcium alone, addition of vitamin K1 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 2.2). Addition of vitamin K1 increased discounted lifetime costs by $4,014, yielding an incremental cost-effectiveness ratio of $9,557/QALY. The probability of lifetime supplementation with vitamin K1, 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 (Figure 2.3b). Based on a US prevalence of 26 million osteopenic women (191), we estimated the budget impact of adding vitamin K1 supplementation to be $104.4 billion. At a threshold of $50,000/QALY, the population expected value of perfect information (EVPI) was $414.9 billion ($15,961/woman) (Appendix: Figure A2.5).
<table>
<thead>
<tr>
<th>Analysis Strategies</th>
<th>Costs, SUS † Mean (95% CrI)</th>
<th>Discounted Life-years Mean (95% CrI)</th>
<th>QALYs ‡ Mean (95% CrI)</th>
<th>Costs, SUS † Mean (95% CrI)</th>
<th>Discounted Life-years Mean (95% CrI)</th>
<th>QALYs ‡ Mean (95% CrI)</th>
<th>Cost ($) / Life-years gained</th>
<th>Cost ($) / QALY gained</th>
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<tbody>
<tr>
<td><strong>Vitamin K2</strong></td>
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<tr>
<td>No supplementation</td>
<td>19190 (12335; 28469)</td>
<td>19.08 (18.76; 19.42)</td>
<td>18.70 (18.22; 19.17)</td>
<td>0.42 (0.32; 0.90)</td>
<td>- 4196 (-9015; 520)</td>
<td>0.43 (0.28; 0.89)</td>
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<tr>
<td>Vitamin D3 with calcium</td>
<td>14994 (9364; 23605)</td>
<td>19.51 (18.71; 20.06)</td>
<td>19.13 (18.28; 19.81)</td>
<td>0.68 (0.73)</td>
<td>8956 (-2618; 23752)</td>
<td>0.73 (0.19; 1.31)</td>
<td>13 171</td>
<td>12 268</td>
</tr>
<tr>
<td>Vitamin K2 with vitamin D3 and calcium</td>
<td>23950 (14306; 38653)</td>
<td>20.19 (19.62; 20.61)</td>
<td>19.86 (19.16; 20.45)</td>
<td>0.14 (0.13)</td>
<td>(- 2618; 23752)</td>
<td>0.73 (0.19; 1.31)</td>
<td>13 171</td>
<td>12 268</td>
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<td><strong>Vitamin K1</strong></td>
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<tr>
<td>No supplementation</td>
<td>19028 (11976; 28066)</td>
<td>19.09 (18.75; 19.43)</td>
<td>18.71 (18.24; 19.15)</td>
<td>-0.42 (-0.22; 0.89)</td>
<td>- 4283 (-9307; 288)</td>
<td>-0.45 (-0.22; 0.89)</td>
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<tr>
<td>Vitamin D3 with calcium</td>
<td>14745 (9269; 22577)</td>
<td>19.51 (18.65; 20.07)</td>
<td>19.16 (18.38; 19.78)</td>
<td>0.42 (0.38)</td>
<td>- 4283 (-9307; 288)</td>
<td>0.45 (-0.22; 0.89)</td>
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<tr>
<td>Vitamin K1 with vitamin D3 and calcium</td>
<td>18759 (5138; 91188)</td>
<td>19.89 (16.77; 20.62)</td>
<td>19.58 (17.41; 20.44)</td>
<td>0.38 (-1.89; 1.41)</td>
<td>- 4283 (-9307; 288)</td>
<td>0.42 (-0.22; 0.89)</td>
<td>10 563</td>
<td>9 557</td>
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<td><strong>Vitamin K2 as a single agent</strong></td>
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<tr>
<td>No supplementation</td>
<td>18987 (12027; 27719)</td>
<td>19.08 (18.76; 19.37)</td>
<td>18.71 (18.22; 19.17)</td>
<td>-0.12 (-0.13; 0.53)</td>
<td>- 4283 (-9307; 288)</td>
<td>-0.14 (-0.13; 0.53)</td>
<td>13 077</td>
<td>12 896</td>
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<tr>
<td>Vitamin D3 with calcium</td>
<td>14764 (8989; 22726)</td>
<td>19.48 (18.64; 20.03)</td>
<td>19.14 (18.28; 19.81)</td>
<td>0.09 (-0.09; 0.53)</td>
<td>- 4283 (-9307; 288)</td>
<td>0.09 (-0.09; 0.53)</td>
<td>13 077</td>
<td>12 896</td>
</tr>
<tr>
<td>Vitamin K2 with vitamin D3 and calcium</td>
<td>24315 (14805; 40554)</td>
<td>20.19 (19.58; 20.59)</td>
<td>19.85 (19.09; 20.41)</td>
<td>0.13 (-0.13; 0.47)</td>
<td>- 4283 (-9307; 288)</td>
<td>0.09 (-0.09; 0.53)</td>
<td>13 077</td>
<td>12 896</td>
</tr>
<tr>
<td>Vitamin K2 alone</td>
<td>24763 (13952; 45966)</td>
<td>20.07 (19.28; 20.52)</td>
<td>19.71 (18.79; 20.31)</td>
<td>0.47 (-0.13; 0.53)</td>
<td>- 4283 (-9307; 288)</td>
<td>0.47 (-0.13; 0.53)</td>
<td>13 077</td>
<td>12 896</td>
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</table>

† Costs and benefits discounted at 3% per year; † Costs in 2009 USD, thousands; ‡ QALY denotes quality-adjusted life year; CrI denotes Credible Interval; D denotes dominance.
Figure 2.2. Scatter plots of 1000 simulated pairs of incremental costs and effects in the cost-effectiveness plane: Vitamin K2 and vitamin K1 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. Figure 2a compares vitamin K2 with vitamin D and calcium to vitamin D with calcium. Figure 2b compares vitamin K1 with vitamin D and calcium to vitamin D with calcium.
Figure 2.3. Cost-effectiveness acceptability curves: Vitamin K2 and vitamin K1 analyses. Probability of cost-effectiveness vs. willingness-to-pay thresholds ($/QALY) of lifetime supplementation with vitamin K2 with vitamin D and calcium (Figure 3a) and vitamin K1 with vitamin D and calcium (Figure 3b), both compared to vitamin D with calcium.
Figure 2.4. Incremental cost-effectiveness ratios (ICERs) by the efficacy of vitamin K2 and vitamin K1. 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. Figure 4a shows that vitamin K2 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 fracture, respectively. Figure 4b shows that vitamin K1 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 fracture, respectively.
2.4.3 Sensitivity analyses

Our results were most sensitive to two assumptions: the efficacy of vitamin K2 and vitamin K1 and their annual costs. The incremental cost-effectiveness ratio exceeded $50,000/QALY if the efficacy of vitamin K2 on hip, vertebral and wrist fractures all decreased by 56-65% (incremental cost-effectiveness ratio: $58,895/QALY) (Figure 2.4a) or the efficacy of vitamin K1 on hip, vertebral and wrist fractures decreased by 12-13% (incremental cost-effectiveness ratio: $50,461/QALY) (Figure 2.4b). The incremental cost-effectiveness ratio also exceeded $50,000/QALY if the mean annual cost of vitamin K2 was $1,812 (base case $865) or the mean annual cost of vitamin K1 was $1,236 (base case $200).

2.5 Conclusions

We evaluated the cost-effectiveness of supplementation with vitamin K2 or vitamin K1 concurrent with vitamin D3 and calcium for the primary prevention of fractures in postmenopausal women initially at low risk of fractures. Compared to vitamin D3 with calcium, supplementation with vitamin K2, 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, addition of vitamin K2 to vitamin D and calcium would represent good value for money.

However, the increments in the costs and benefits with vitamin K2 are associated with large uncertainty (Table 2.1). 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 we did find significant increments in survival and QALYs, our estimates for the efficacy of vitamin K2 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 K2 trials (56) and the lack of evidence regarding fracture reductions in Caucasian populations. Our sensitivity analysis also showed that the efficacy of vitamin K2 is one of the major determinants of the 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 K2 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 K2 was sensitive to the cost of vitamin K2. The market price of vitamin K2 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 K1, vitamin D and calcium found that addition of vitamin K1 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 (67). The difference in our incremental cost-effectiveness ratio estimates likely results from differences in study design, base case profiles and model structures. They compared 5mg/day vitamin K1 to no intervention in 50-year-old women with osteoporosis over 10 years (67). We used a longer time horizon (50 years) and modeled vitamin D with calcium in postmenopausal women initially without osteoporosis.

In our study, vitamin K1 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 K1 (Table 1) (76;103). Stevenson et al examined the uncertainty around the cost-effectiveness of vitamin K1 vs. alendronate using expected value of sample information (EVSI) (66;67). EVSI is another value of information method used to estimate the expected size and expected cost of the perfect trial (76). At a £30,000 [$48,650]/QALY threshold, Stevenson et al estimated that a future vitamin K1 trial would include 2000–5000 participants per arm (£1111.3 [US$1,802] per participant) (66;67). However, as the expected net gain (ENG) was not calculated and was not compared to the EVSI and actual costs of the vitamin K1 trial (103), the question remains whether to adopt vitamin K1 based on current evidence or to undertake another trial. Overall, our vitamin K2 and vitamin K1 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 (14). 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 (13;192). 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) (13;193;194). 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 K2 was the same in Japanese and Caucasian populations due to the lack of data on fractures for vitamin K2 in Caucasian populations. In addition, the efficacy of vitamin K1 was based on the results of a single randomized-controlled trial where fractures were only a secondary endpoint (60). 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 (20). Both anabolic and anti-resorptive effects on bone have been ascribed to vitamin K based on its several functions such as $\gamma$-carboxylation of 3-glutamic acid residue to enable functioning of osteocalcin (38-40), regulation of the transcription of bone-specific genes to enable the expression of osteoblastic markers (42;43), inhibition of the nuclear factor kappa B and modulation of the expression of interleukin-6 and osteoprotegerin to modify bone turnover (20;44;45), and inhibition of prostaglandin E2 to reduce bone resorption (42;46;47). Some authors argue that through these actions vitamin K may improve bone quality and bone strength without increasing BMD (17;42). Finally, we did not directly model a comparison of vitamin K2 to vitamin K1.
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.
Chapter 3
Uncertain treatment effects of the K vitamins on BMD and fractures in postmenopausal women – an indication for further research: A systematic review and meta-analyses

3. Study 2

3.1 Abstract

Introduction: Controversies about the effects of vitamin K2 and vitamin K1 on BMD and fractures have arisen from the epidemiologic evidence. We systematically reviewed the current literature in postmenopausal populations to examine the uncertainty around the effects of the K vitamins on BMD or fractures in current and future trials.

Methods: We systematically searched electronic databases (Medline, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, AMED, International Pharmaceutical Abstracts: 1947-Dec 2012) and bibliographies. We included RCTs in postmenopausal women that assessed the effects of vitamin K2 or vitamin K1 on BMD at the lumbar spine (LS), femoral neck (FN), total hip (TH) and distal radius (DR) or on the risk of any clinical, vertebral or non-vertebral fractures and with a minimum follow-up of 12 months. Three reviewers assessed the methodological quality of RCTs using the Cochrane Risk of Bias tool. We used both Bayesian and frequentist meta-analysis approaches to estimate the treatment effects of the K vitamins on BMD or fractures in current and future trials. Our outcomes were the mean differences in BMD (MD, %), the population odds ratios (OR) and the probabilities of benefits of the K vitamins. We used 95% credible and confidence intervals (95%CrI/CI) to address the uncertainty around the mean treatment estimates.

Results: We reviewed 146 potentially eligible RCTs and synthesized the evidence from 19 trials, 12 comparing vitamin K2 (0.36-45mg/day in 6026 women), 5 comparing vitamin K1 (0.08-5mg/day in 1188 women) and 2 comparing both vitamins (554 women) to controls. Vitamin K2 increased LS BMD by 1.2% (Bayesian 95% CrI: 0.0-2.5; Classical 95% CI: 0.2,2.3), but this positive effect was highly uncertain in a future trial (Bayesian future MD: 1.2%, 95%CrI: -2.3, 4.8). The probability of showing 1% increase in LS BMD was 88% in current and
67% in future trials. Vitamin K2 had no effect on FN and TH BMDs, with the probabilities of showing 1% increase in BMD in current and future trials of 13% and 16% (FN BMD) and 0.005% and 2% (TH BMD). Vitamin K1 had almost zero effect on LS and TH BMDs and a slightly greater and an uncertain effect on FN BMD (Bayesian MD: 0.7%, 95%CrI: -0.7, 2.4). The probabilities of showing 1% increase in BMD in current and future trials were 3% and 11% for LS BMD, 7% and 11% for TH BMD and 62% and 56% for FN BMD. The protective effects of vitamin K2 on all clinical fractures (population OR= 0.6 [95%CrI: 0.2, 1.4] and future OR=1.1 [95%CrI: 0.0, 5.3]), vertebral and non-vertebral fractures were inconclusive. However, the probabilities of decreasing the odds of fractures by 20% in current trials were 81%, 75% and 87% for all clinical, vertebral and non-vertebral fractures; in future trials, the corresponding probabilities were 66%, 62% and 72%.

**Conclusion:** In the univariate meta-analyses, we showed a small and uncertain effect of both K vitamins on BMD. The protective effect of vitamin K2 on fractures is inconclusive and should be examined in large high-quality RCTs before the K vitamins are recommended for the prevention and treatment of osteoporosis and fractures in postmenopausal women.

**Keywords:** vitamin K, meta-analysis, Bayesian methods, bone density, fractures, postmenopausal

### 3.2 Introduction

Several controversies about the effects of the K vitamins on BMD and fractures have arisen from the epidemiologic evidence. Vitamin K2 has been shown to be protective of bone loss in elderly Japanese women (56). In contrast, vitamin K1 has been shown to have no effect on BMD in postmenopausal Caucasian women (58;60-63). Despite the differences in study populations or vitamin K preparations, the majority of trials that examined fractures reported 55-80% risk reductions of clinical fractures in both Japanese (56) and Caucasian populations (60). The highly positive effects of the K vitamins on fractures have augmented the controversy because the efficacy estimates are equal to or are even better than the efficacies of pharmacologic therapies (17;56). In addition, other differences have been noticed among the vitamin K1 and the vitamin
K2 trials. More specifically, the vitamin K1 trials were associated with high heterogeneity in terms of a daily dose. Some trials used a small dose of 90-120 µg daily, following the current dietary recommendations (27;61). Other trials used a larger vitamin K1 dose of 500 µg daily, which is the amount achievable by dietary intake (20;27;61), or of 1000 µg daily, which is the amount necessary to achieve maximal carboxylation of osteocalcin (63;195). In contrast, a very large daily dose of vitamin K2 (45 mg) was used in most trials in Asian populations because vitamin K2 is a pharmacologic therapy for osteoporosis in Japan and some parts of Asia (17).

Considerable heterogeneity between the trials is also present in terms of duration of treatment, variable baseline risks of fractures and differences in methodological quality of the studies (42;56). Thus, despite the accumulation of new evidence in postmenopausal populations over the past decade, a gap in knowledge has remained regarding the possible effectiveness of vitamin K on bone outcomes. If vitamin K is able to improve bone health even marginally, it may become an affordable and a potentially cost-effective primary strategy for the prevention of osteoporosis and fractures together with vitamin D and calcium (196).

Bayesian random-effects meta-analysis can be used to synthesize the evidence and calculate the probabilities of the benefits of vitamin K regarding fracture reduction or BMD increase (80;115). It can be also used to generate prediction intervals for the effect of vitamin K in future trials (80). The Bayesian predictions and probabilities could be further employed to explore the need for future trials. Therefore, we systematically reviewed the current literature in postmenopausal populations. We used both Bayesian and frequentist meta-analysis approaches to estimate the treatment effects of vitamin K2 and vitamin K1 on BMD or fractures in current trials. Using Bayesian models, we estimated the true treatment effect of vitamin K in future trials. From the Bayesian posterior distributions, we determined the probabilities of benefits of the K vitamins in current and future trials for each bone outcome.

3.3 Methods

3.3.1 Literature search

We systematically searched electronic databases, Medline, EMBASE plus ClassicEMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, AMED and International Pharmaceutical Abstracts, from their inception to December 31, 2012. The search strategies, designed with help of a university hospital librarian, included a
combination of key words, MeSH terms and text words related to bone, bone diseases and fractures, further combined with the generic and trade names of vitamin K2 and vitamin K1 preparations (Appendix). In addition, we manually searched conference proceedings (i.e., ASBMR, IOF) and screened reference lists of all obtained papers. We a priori designed the study (protocol presented in the Appendix) and used guidelines of the PRISMA statement to report the results (197). Bayesian meta-analysis was design and reported according to the ROBUST criteria (198). Our study was approved by the Research Ethics Boards of University Health Network and the University of Toronto.

3.3.2 Study selection

We included RCTs that compared oral vitamin K2 or vitamin K1 supplements (alone or included in multivitamin preparations) to control treatments in postmenopausal women or women aged 45 years and over; the included trials had to report changes in BMD by Dual-energy X-ray absorptiometry (DXA) or new fractures after a minimum follow-up of 12 months. Two reviewers (OGV, ZA) independently identified and evaluated articles for eligibility. Disagreements were reviewed by three reviewers (OGV, ZA and AC) and were resolved by consensus.

3.3.3 Outcomes

Our two main outcomes were changes in BMD and incidence of fractures. We examined changes in BMD at most commonly measured skeletal sites: the lumbar spine (L1-L4 or L2-L4), femoral neck, total hip and radius (distal and ultra-distal). We extracted relative changes in BMD and absolute changes in areal BMD (g/cm2). Relative changes in BMD were reported using the following effect measures: 1) arithmetic mean percent change from baseline in each group; 2) difference between the two groups in arithmetic mean percent change from baseline; 3) arithmetic mean percent change from baseline in BMD T-score in each group; and, 4) geometric mean percent change from baseline in each group, calculated in one trial (63). Absolute changes in areal BMD (g/cm2) were measured as mean change from baseline in each group and mean difference between the two groups. Incident fractures were extracted as a number or rate of new fractures and were classified into all reported fractures, vertebral fractures (as confirmed by X-ray), non-vertebral fractures, hip, arm (including wrist) and other fractures. If outcomes were
measured at multiple time points, we extracted data reported for the last follow-up (according to the entry criteria: at least 12 months).

3.3.4 Quality assessment

Two reviewers (OGV, ZA) independently assessed methodological quality of the trials using the Cochrane Risk of Bias tool version 5.0 (199;200). This checklist addresses five major types of biases that occur in experimental studies: selection bias (randomization and allocation concealment), performance and detection bias (blinding of participants, providers and outcome assessors), attrition bias (assessment of incomplete data including intention-to-treat analysis) and publication bias (199;200). Discrepancies in ratings between the two reviewers were discussed with the third reviewer (AC) and were resolved by consensus. We classified overall within-trial bias into three categories: low, high and unclear (Appendix: Table A3.2). If the procedures to prevent selection bias and performance bias were adequately reported, and if intention-to-treat analysis was adequately performed, trials were assigned the category of low bias because evidence suggests these types of biases as the most important (201). In contrast, if a trial was associated with all three types of bias, the within-study bias was classified as high (Appendix 3.7.1: Table A3.2). The unclear category was assigned to trials that omitted to clearly report or omitted to conduct procedures to prevent selection, performance or attrition bias. In addition, for each trial, loss-to-follow-up (in %) was calculated.

3.3.5 Data abstraction

For data collection, we used electronic data abstraction forms, pilot-tested for completeness, accuracy and feasibility. Two reviewers (OGV and ZA) independently extracted data on the outcomes, including effect measures and recalculations of measures of dispersion (e.g., standard deviations) that were not directly reported in the papers. When necessary, measures of dispersions were estimated from the graphs in published papers (please see examples in the Appendix: Figure A3.2). Extraction of outcome data was repeated at two time points; the second data extraction served to double-check discrepancies in data collection between the reviewers. We averaged the values of persistently discrepant outcome data when the discrepancies were small and considered to be due to measurement of graphs and not due to miscalculation. All extracted data were reviewed by the third reviewer (AC). One author (OGV) abstracted data on patients’ characteristics (age, body mass index, comorbidities,
osteoporosis at baseline [baseline BMD] and prevalent fractures), their baseline dietary intakes of vitamin D and calcium, type and dose of vitamin K and control treatments, and the trials’ design, duration and year of publication.

3.3.6 Quantitative synthesis: Univariate meta-analysis

We performed univariate random-effects Bayesian and classical meta-analyses to evaluate the effects of vitamin K2 and vitamin K1 on BMD or fractures. We used random-effects models regardless of the amount of between-study heterogeneity as the between-study variance is often underestimated in small meta-analyses (202;203); also, the fixed-effects and random-effects analyses provide the same results in case of homogeneity (111;113).

Classical meta-analysis was done using the weighted inverse variance method (111;113). We estimated the pooled mean differences (MD) for continuous outcomes, and population log-odds ratios and odds ratios (OR) for binary outcomes, including their 95% confidence intervals (CI). Continuity corrections (i.e., adding 0.5 to each treatment cell) were applied in trials containing study arms with zero events (111;113). Statistical heterogeneity was assessed with Cochran’s Q test and was quantified using the I² statistic (203). The estimate of between-study variance, denoted as \( \tau^2 \), was approximated by the method of moments (80;111;113).

Bayesian meta-analysis was performed using hierarchical random-effects normal and binomial models (115). Bayesian random-effects meta-analyses have to incorporate two priors, one on the mean treatment effect and one on the between-study variance, to generate the posterior distributions of the mean treatment effects (115). We specified the best-fitting non-informative prior on the between study variance (as determined by residual deviance, see section on influence analysis) and a uniform non-informative prior on the mean treatment effect. The main outputs of our Bayesian meta-analysis pertinent to the pooled mean treatment effect were the population mean treatment effect in current studies (i.e., pooled mean difference denoted as MD [i.e., % change in BMD], pooled log-odds ratio or population OR) and the predictive distributions of true treatment effect in a future study (i.e., future MD, future log-odds ratio, future OR). The predictive distributions were estimated by sampling from the posterior distributions of the treatment effects of current studies and as such, they incorporated variability from two sources: first, the variance around the pooled treatment effect and second, the between-study variance \( \tau^2 \) (115). Samples from the posterior distributions of each parameter were
obtained by the Markov chain Monte Carlo method (115). From these samples, the median was estimated by the 50th percentile, and equal-tailed ninety-five percent credible intervals (95% CI) were created from the 2.5th and 97.5th percentiles (115).

The probabilities of benefit of the K vitamins on BMD were defined as the probabilities of showing any (>0%) or a 1%, 3% or 5% increase in BMD; for the effects on fractures, the posterior probabilities of benefit were calculated for the population OR being less than 1 (any benefit) or equal to 0.95, 0.9, 0.8 or 0.7. These effect sizes are comparable to the ranges of treatment effects attained with vitamin D and calcium or with alendronate (175;204-207).

Several systematic reviews showed that the use of vitamin D with calcium for one year was associated with a 1% increase in BMD at the lumbar spine, hip or the femoral neck (205;207). The use of vitamin D and calcium for up to seven years was associated with a 5-20% reduction of hip (OR:0.80-0.84), vertebral (OR=0.9), non-vertebral (OR=0.95) or all fractures (OR:0.8-0.9) (204-207). Tang et al showed that the reduction of all fractures was 24% (RR: 0.76, 95%CI: 0.67-0.87) in patients who were highly compliant (the use of vitamin D with calcium ≥80%) (207). The alendronate use for 2-4 years was associated with a 3-8% increase in BMD at the lumbar spine or total hip (208) and a 20-40% reduction of hip, all non-vertebral or vertebral fractures (175). As a result, our definition of clinically important benefits with vitamin K was based on the treatment efficacies of vitamin D and calcium: an increase in BMD of 1% (MD=1%) or a 20% reduction in odds of all fractures (OR= 0.8) was considered clinically important. Accordingly, we calculated the probabilities of important benefits for these effect sizes (MD=1 and OR=-0.8). We additionally explained the posterior probabilities of benefits with vitamin K using odds. For example, a probability of 75% is evidence weighted 75:25 or 3 to 1 in favor of benefit. We assumed that a probability of benefit greater than 50% indicates a benefit from the treatment with vitamin K (145).

Few vitamin K trials included multiple arms comparing the K vitamins alone or vitamin K concurrent with vitamin D to several control groups. Our reference analysis included no adjustment for multi-arm trials. In the case of multiple vitamin K and control arms, we compared the data of the arm with vitamin K alone to an available control group giving the priority to placebo or no treatment followed by the control groups including vitamin D plus calcium or vitamin D. In sensitivity analysis, we estimated the pooled treatment effects by
combining the data of multiple control arms with the weighted mean approach (113;199) and made comparisons with the corresponding results of the reference analysis (Table A3.3).

3.3.7 Bayesian meta-regression

To explore large between-study heterogeneity, we performed meta-regressions using Bayesian random-effects models. Due to the small numbers of combined trials, we performed separate univariate meta-regressions that included one categorical variable at a time. For example, we examined differences in study populations. As there was a clear division in patient characteristics among the vitamin K2 studies, we were able to separate the trials into two categories: one included Asian osteoporotic patients and another included Caucasian non-osteoporotic patients. We also examined the following covariates: 1) dose of the K vitamins (vitamin K2 studies: low:< 45mg/day vs. high:≥ 45 mg/day; vitamin K1 studies: low:< 1mg/day vs. high:≥ 1 mg/day); 2) duration of treatment (12 months vs. > 12 months); 3) risk of bias (within-trial bias: low vs. unclear or high; allocation concealment: adequate vs. inadequate/unclear and double-blinding: adequate vs. inadequate/ unclear); and, 4) baseline rate of prevalent fractures. In the fracture models adjusting for prevalent fractures, we calculated break-even points or the baseline probabilities of fractures below which vitamin K had the zero effect or was harmful (149).

3.3.8 Influence analysis and sensitivity to the choice of prior on the between-study variance

We performed influence diagnostic analysis to determine which trials had the biggest effect on the pooled estimates and heterogeneity (209). We also performed a sensitivity analysis on the choice of the prior on \( \tau^2 \) in Bayesian meta-analyses. We assessed model fit of eight priors on \( \tau^2 \) that were proposed in the literature (138;141;210). We used total residual deviance as a goodness-of-fit measure to determine the best-fitting prior on \( \tau^2 \) for each meta-analysis, which we further used for the reference meta-analyses.

3.3.9 Publication bias

We used Egger’s linear regression test to examine funnel plot asymmetry and check for small study bias (111;113;152). We also used the trim and fill method to impute missing studies and examine publication bias (111;113;152).
3.3.10 Computations

We performed classical meta-analyses, calculated $I^2$ statistics and the approximations of $\tau^2$ (111;113) using RevMan 5 (the Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen, Denmark, 2008; packages: meta and metaphor (209)) and R 2.13.1 (R Foundation for Statistical Computing, Vienna, Austria, 2008). The influence analysis and assessment of publication bias were done in R (209). Tests of significance were 2-sided and regarded as statistically significant if $p<0.05$. The Bayesian meta-analyses, meta-regressions and sensitivity analyses to the choice of prior on $\tau^2$ were done in WinBUGS 1.4.3 (Imperial College and MRC, UK, 2007) (211) and R 2.13.1 (packages: rjags and R2BUGS (212)). The Bayesian analyses were all done to the same standard: we ran three Markov chains starting at dispersed sets of initial values for a total of 300,000 iterations, of which the first 30,000 were discarded. Convergence of the chains was checked by Brooks–Gelman–Rubin (BGR) plots and the Gelman–Rubin statistic (213). The chains were considered to have converged when the Gelman–Rubin statistic reached 1 (213). The WinBUGS code is presented in the Appendix.

3.4 Results

Out of 146 potentially eligible full-text articles, 19 articles were included in the systematic review (Figure 3.1) (59-65;71;168;170;171;214-221). These 19 RCTs included 7768 postmenopausal women. In 12 trials, 6026 women were allocated to vitamin K2 or control (59;65;71;168;170;171;215-218;220;221), in five trials, 1188 women were allocated to vitamin K1 or control (60-62;214;219), while in two trials, 554 women were allocated to either vitamin K2, vitamin K1 or placebo (63;64) (Table 3.1). Detailed results regarding the literature search and characteristics of the included trials are presented in the following section, Table 3.1 and in the Appendix.

3.4.1 Study characteristics

All but one vitamin K2 trial (59) used menaquinone-4 supplements in a daily dose of 45 mg (Table 3.1). The vitamin K1 trials used phylloquinone supplements in a daily dose ranging from 0.08-5 mg (60-62;214;219), while the two trials comparing both vitamin K preparations used daily doses of 45 mg and 0.1 mg for vitamin K2 (64;222), and 1 mg and 0.1 mg for vitamin K1.
(64;222) (Table 3.1). The control groups were diverse and included placebo, no treatment, vitamin D, calcium and multivitamin preparations. One trial included hormone replacement therapy among multiple control groups (216) and another trial used alendronate as control (215), but as mentioned in the methods section, these data were not meta-analyzed. One vitamin K2 trial (59) and two vitamin K1 trials (60;61) described adequate concealment, randomization, blinding and analysis of incomplete data and were assigned low risk of bias (Table 3.1 and Appendix 1: Table A3.2). Two vitamin K2 (59;218) and all vitamin K1 trials (60-62;214;219) and one trial including both preparations (222) reported adequate blinding of patients and health care providers. Three vitamin K2 trials (59;168;171), two vitamin K1 trials (60;61) and one trial including both vitamin K preparations (222) performed an intention-to-treat analysis. A BMD outcome was reported in the majority of trials (59-64;71;168;170;171;214-221); in the majority, it was measured as the mean percent change from baseline (59-61;63;71;168;170;171;214;216-220) (Appendix: Table A3.1). Fractures were reported in five trials (60;65;168;170;171), of which only one compared vitamin K1 (60). Duration of the trials varied from 12-36 months; on average, those reporting BMD were shorter. In terms of the characteristics of study populations, ten of 12 vitamin K2 trials were done in Asian populations (Japanese and Taiwanese) (Table 3.1). The average age of women ranged from 53-68 years in the vitamin K2 trials reporting BMD and 66-74 years in those reporting fractures. Most of the vitamin K2 participants had osteoporosis at baseline (defined by a baseline areal BMD< 700 g/cm2 at one or multiple skeletal sites – lumbar spine, femoral neck or total hip). All vitamin K1 trials and two trials comparing both vitamin K supplements included Caucasian, healthy and non-osteoporotic women whose mean age ranged from 55-68 years.
Figure 3.1. PRISMA flow diagram: Vitamin K2 and vitamin K1 trials
Table 3.1. Characteristics of vitamin K2 and vitamin K1 trials included in the systematic review and their risk of bias

<table>
<thead>
<tr>
<th>Trial</th>
<th>Single-center, duration, months</th>
<th>Bias†</th>
<th>Trial population</th>
<th>Interventions (daily dose)</th>
<th>Outcomes</th>
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<td>Concealment adequate</td>
<td>Blinding</td>
<td>ITT performed †</td>
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<td>Trial</td>
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<td>Bias†</td>
<td>Trial population</td>
<td>Interventions (daily dose)</td>
<td>Outcomes</td>
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</tbody>
</table>

† Selected items of the Cochrane’s Risk of Bias tool (Appendix); LFU= loss-to-follow up in %; HRT=hormone replacement therapy; NR= not reported; ‡ Age averaged across the groups; ¹ non-fractured, ² fractured, 3 women-only groups; * in a multivitamin preparation; § LFU at 36 months; ‡ search updated in March 2012 and the new study assessed by one reviewer (OGV); ‡ 3 interventions were given as fortified low fat milk/yogurt.
3.4.2 Vitamin K2

Effects on BMD

Bayesian and classical meta-analyses included nine vitamin K2 trials (59;71;168;170;171;216-218;220) and the Binkley trial (the vitamin K2 and control arms)(63). All trials reported the mean percent changes in BMD from baseline at one of the four skeletal sites. Both types of meta-analyses resulted in similar estimates of the mean difference (MD) (Figure 3.2). Vitamin K2 increased the mean BMD at the lumbar spine by 1.2% in the meta-analyses of eight trials including 1332 women (Bayesian MD: 1.24%, 95% CrI: 0.00 to 2.53; Classical MD: 1.20%, 95%CI: 0.15 to 2.25; p=0.01, I²=84%) (Figure 3.2a). In the influence analysis, this increase was not statistically significant after omitting the trial by Iwamoto (216) (0.90%, 95%CI: -0.10 to 1.90, I²=80%), but it remained statistically significant after omitting the trial by Binkley (63) (1.50%, 95%CI: 0.50 to 2.62, I²=79%). Bayesian synthesis of the current evidence indicated a 88% probability of 1% increase in BMD at the lumbar spine (Table 3.2). The positive effect of vitamin K2 was highly uncertain in a future trial (future MD: 1.20%, 95%CrI:-2.30 to 4.80), with a 67% probability of 1% increase in BMD.

In a meta-regression analysis, the effect of vitamin K2 on BMD at the lumbar spine was stronger in older Asian osteoporotic women (regression slope: -2.45%, 95%CrI: -4.46 to -0.51). In a subgroup analysis, an actual increase in BMD in this population was 2.2% (95%CrI: 0.10 to 3.62), with 86% and 74% probabilities of having a 1% increase in BMD in current and future trials (Figure 3.3). In contrast, in Caucasian women, there was a mean percent decrease in BMD of -0.2% (95%CrI: -1.70 to 1.34) (Figure 3.3); the probabilities of showing a MD of 1% were small (14% and 26% in current and future trials). In separate univariate meta-regressions, the effects of dose, study duration, allocation concealment, blinding and risk of bias on change in BMD were weak. The respective regression slopes were: 1) dose: 1.45%, 95%CrI: -2.25 to 5.33; 2) study duration: 0.53%, 95%CrI: -2.04 to 3.20; 3) allocation concealment: -0.87%, 95%CrI: -3.53 to 1.72; 4) blinding: 1.53%, 95%CrI: -4.11 to 0.99; and, 5) risk of bias: 1.44%, 95%CrI: -2.13 to 5.17. In a subgroup analysis, women on high–dose (45 mg/day) vitamin K2 were more likely to benefit, with 92% and 71% probabilities of having a 1% increase in BMD in current and future trials. The participants of trials with bias in two or more categories or open-label trials also had a greater chance to benefit from vitamin K2. For studies with high or unclear risk of bias, the probabilities of 1% increase in current and future trials were 93% and 70% and for open-label trials, they were 96% and 79%.
The effects of vitamin K2 on BMD at the femoral neck and total hip were inconclusive (Figures 3.2b and 3.2c). These were based on meta-analyses of two trials in 659 women for femoral neck BMD (59;71) and three trials in 914 women for total hip BMD (59;63;71). The probabilities of showing a 1% increase in these BMD sites were small (0% for total hip and 13% for femoral neck) (Table 3.2).

In contrast, based on the meta-analyses of two trials in 179 women (170;171), vitamin K2 significantly increased BMD at the distal radius (Bayesian MD: 1.55%, 95% CrI: 0.23 to 2.88; Classical MD: 1.54%, 95%CI: 0.80 to 2.28; p<0.0001, I²=0%). The effect on BMD in a future trial was still positive but it ranged from a 0.4% loss to a 3.6% increase in BMD (Figure 3.2d). The probabilities of showing a 1% increase in BMD at the distal radius were 96% and 93% in current and future trials (Table 3.2).

Two one-year trials (64;215) and one two-year trial (221) were not included in the quantitative synthesis. These trials were associated with high risk of bias and measured changes in areal BMD (Table 3.1 and Appendix 3.1). The first one-year trial by Hirao et al (215) compared vitamin K2 plus alendronate to alendronate alone in 48 Japanese postmenopausal women. Vitamin K2 combined with alendronate improved a mean BMD T-score at the femoral neck by 6 ± 8% (vs. control: 4 ± 9%, p=0.03); but, it did not significantly increase mean BMD T-scores at the lumbar spine and total hip. The second one-year trial by Mochonis et al (64) randomized 173 postmenopausal women to 0.1 mg of vitamin K2 (MK-7), 0.1 mg of vitamin K1 (both concurrently given with vitamin D and calcium), vitamin D and calcium alone or no supplementation. Compared to a non-supplemented group, both vitamin K groups had statistically significant increases in BMD at the lumbar spine at 12 months (mean changes: 0.006g/cm² [95%CI: -0.018 to 0.026] in vitamin K2 and 0.016g/cm² [95%CI: -0.005 to 0.036] in vitamin K1 and -0.032 g/cm² [95%CI: -0.046 to -0.011] in control). In a two-year trial, Yasui et al randomized 34 Japanese postmenopausal women to 45 mg MK-4 or 45 mg MK-4 plus vitamin D3 (221). At baseline, the participants’ average age was 53 years and they had osteopenia or osteoporosis (BMD < 0.809 g/cm²) (221). In the group treated with both vitamin K2 and vitamin D3, no statistically significant change in BMD at the lumbar spine was found (areal BMD g/cm²: 0.728±0.056 [baseline] vs. 0.707±0.058 [2 years]), while in the group treated with vitamin K2 only, a statistically significant decrease in BMD was shown (areal BMD g/cm²: 0.743±0.052 [baseline] vs. 0.685 ±0.04 [2 years]).
Effects on fractures

In Bayesian meta-analysis of four heterogeneous trials in 4384 women (65;168;170;171), vitamin K2 was associated with reductions of all reported fractures, non-vertebral and vertebral fractures, corresponding to the population ORs of 0.61, 0.47 and 0.67 (Figure 3.4). From a frequentist perspective, these reductions were not statistically significant (e.g., all fractures: population OR=0.66, 95%CI: 0.43 to 1.03, p=0.07, I²=74%). In influence analysis, the trial by Inoue was shown to have the most influence on study results; after omitting this study, the population OR became statistically significant (the population OR changed from 0.66 [95%CI: 0.43 to1.03] to 0.34 [95%CI:0.20 to 0.57]). For all types of fractures, predictive distributions of future OR were wide and uncertain with the 95% CrI limits ranging from 0 to 5 (Figure 3.4 and Appendix: Figure A3.3). For non-vertebral and vertebral fractures, the probabilities of showing the OR of 0.80 were 87% and 75% in current trials, and 72% and 62% in future trials; based on current evidence, the odds of clinically important benefits were 3 or 4 to 1 (Table 3.3). The odds of clinically important benefits for hip and arm (including wrist) fractures were very high, around 9 to 1, but these estimates were based on the data from two studies (168;171).

We found negative but uncertain relationships between the baseline risk of fracture and the effect of vitamin K2. Higher reductions of fractures in women at greater baseline risks resulted in insignificant regression slopes for all clinical (change in log-odds:-0.56, 95%CrI:-2.09 to 0.87), non-vertebral (change in log-odds:-3.71, 95%CrI:-27.01 to 15.33) and vertebral fractures (-0.47, 95%CrI:-1.89 to 0.78). Vitamin K2 was associated with a reduction in odds of all clinical fractures if a baseline fracture probability was above 13%. The effect of vitamin K2 on non-vertebral and vertebral fractures was positive if the baseline fracture probabilities were over 3% (non-vertebral) and over 11% (vertebral).
Figure 3.2a. Forest plot on mean percent changes in BMD at the lumbar spine – vitamin K2 vs. control: Bayesian and classical random-effects meta-analyses. CrI denotes credible interval and CI denotes confidence interval. Bayesian mean percent differences in BMD (Bayesian MD) for each trial are represented by the black circles; the black solid lines through the circles are 95%CrIs. Classical MDs for each trial are represented by the grey circles; the grey dashed lines through the circles are 95%CIs. The black and the blue squares represent Bayesian pooled MDs for the current and a future trial, with the corresponding 95%CrIs. The best-fitting prior on the between-study variance (according to residual deviance) was used to generate Bayesian pooled MDs in current and new trials. The diamond is the estimated classical pooled MD; the length of the diamond reflects 95%CI around the pooled estimate.
Figure 3.2b. Forest plot on mean percent changes in BMD at the femoral neck – vitamin K2 vs. control: Bayesian and classical random-effects meta-analyses. CrI denotes credible interval and CI denotes confidence interval. Bayesian mean percent differences in BMD (Bayesian MD) for each trial are represented by the black circles; the black solid lines through the circles are 95%CrIs. Classical MDs for each trial are represented by the grey circles; the grey dashed lines through the circles are 95%CIs. The black and the blue squares represent Bayesian pooled MDs for the current and a future trial, with the corresponding 95%CrIs. The diamond is the estimated classical pooled MD; the length of the diamond reflects 95%CI around the pooled estimate.
### Figure 3.2c.

Forest plot on mean percent changes in BMD at the total hip – vitamin K2 vs. control: **Bayesian and classical random-effects meta-analyses**. CRI denotes credible interval and CI denotes confidence interval. Bayesian mean percent differences in BMD (Bayesian MD) for each trial are represented by the black circles; the black solid lines through the circles are 95%CRIIs. Classical MDs for each trial are represented by the grey circles; the grey dashed lines through the circles are 95%CIs. The black and the blue squares represent Bayesian pooled MDs for the current and a future trial, with the corresponding 95%CRIIs. The diamond is the estimated classical pooled MD; the length of the diamond reflects 95%CI around the pooled estimate.
Figure 3.2d. Forest plot on mean percent changes in BMD at the distal radius – vitamin K2 vs. control: Bayesian and classical random-effects meta-analyses. CrI denotes credible interval and CI denotes confidence interval. Bayesian mean percent differences in BMD (Bayesian MD) for each trial are represented by the black circles; the black solid lines through the circles are 95%CrIs. Classical MDs for each trial are represented by the grey circles; the grey dashed lines through the circles are 95%CIs. The black and the blue squares represent Bayesian pooled MDs for the current and a future trial, with the corresponding 95%CrIs. The diamond is the estimated classical pooled MD; the length of the diamond reflects 95%CI around the pooled estimate.
## Table 3.2. Probabilities of benefits of the K vitamins on BMD at different skeletal sites

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<tr>
<th>Mean % Increase</th>
<th>Vitamin K2</th>
<th></th>
<th>Vitamin K1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Current trials</td>
<td>Future trials</td>
<td>Current trials</td>
</tr>
<tr>
<td>&gt; 0 %</td>
<td>LS BMD</td>
<td>0.97</td>
<td>0.77</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>FN BMD</td>
<td>0.68</td>
<td>0.66</td>
<td>0.23</td>
</tr>
<tr>
<td>1 %</td>
<td>LS BMD</td>
<td>0.88</td>
<td>0.13</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>FN BMD</td>
<td>0.67</td>
<td>0.16</td>
<td>0.02</td>
</tr>
<tr>
<td>3 %</td>
<td>LS BMD</td>
<td>0.003</td>
<td>0.002</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>FN BMD</td>
<td>0.22</td>
<td>0.007</td>
<td>0.00</td>
</tr>
<tr>
<td>5 %</td>
<td>LS BMD</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>FN BMD</td>
<td>0.03</td>
<td>0.002</td>
<td>0.00</td>
</tr>
</tbody>
</table>

LS= lumbar spine, FN= femoral neck, TH= total hip, DR= distal radius.
Figure 3.3. Bayesian meta-regression analyses: Vitamin K2 and vitamin K1 and their effects on BMD at the lumbar spine in subgroups for various characteristics of the pooled trials. CrI denotes credible interval, OP osteoporosis at baseline, NA non applicable. § Low-dose vitamin K: <45mg/day (K2) or <1mg/day (K1), high-dose vitamins K: ≥45mg/day (K2) or ≥1mg/day (K1).
Figure 3.4. Forest plots on all clinical fractures, non-vertebral, vertebral, hip and arm (including wrist) fractures – vitamin K2 vs. control: Bayesian and classical random-effects meta-analyses. CrI denotes credible interval and CI denotes confidence interval. The best-fitting prior on the between-study variance (according to residual deviance) was used to generate Bayesian ORs in current and new trials. Bayesian odds ratio (Bayesian OR) for each trial are represented by the black circles; the black solid lines through the circles are 95%CrIs. Classical OR for each trial are represented by the grey circles; the grey dashed lines through the circles are 95%CIs. The black and the blue squares represent Bayesian population OR and future OR, with the corresponding 95%CrIs. The diamond represents population ORs estimated in the classical meta-analyses.
Table 3.3. Probabilities of benefits of vitamin K2 on fractures

<table>
<thead>
<tr>
<th>Fractures</th>
<th>Probability of Effect: OR&lt;1</th>
<th>Probability of Effect: OR=0.95</th>
<th>Probability of Effect: OR=0.90</th>
<th>Probability of Effect: OR=0.80</th>
<th>Probability of Effect: OR=0.70</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Current Studies</td>
<td>Current Studies</td>
<td>Current Studies</td>
<td>Current Studies</td>
<td>Current Studies</td>
</tr>
<tr>
<td></td>
<td>Future Studies</td>
<td>Future Studies</td>
<td>Future Studies</td>
<td>Future Studies</td>
<td>Future Studies</td>
</tr>
<tr>
<td>All clinical</td>
<td>0.91</td>
<td>0.90</td>
<td>0.87</td>
<td>0.81</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>0.72</td>
<td>0.70</td>
<td>0.66</td>
<td>0.60</td>
</tr>
<tr>
<td>Non-Vertebral</td>
<td>0.94</td>
<td>0.93</td>
<td>0.91</td>
<td>0.87</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>0.78</td>
<td>0.77</td>
<td>0.76</td>
<td>0.72</td>
<td>0.68</td>
</tr>
<tr>
<td>Vertebral</td>
<td>0.89</td>
<td>0.87</td>
<td>0.84</td>
<td>0.75</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>0.72</td>
<td>0.70</td>
<td>0.67</td>
<td>0.62</td>
<td>0.56</td>
</tr>
<tr>
<td>Hip</td>
<td>0.98</td>
<td>0.97</td>
<td>0.97</td>
<td>0.97</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>0.94</td>
<td>0.93</td>
<td>0.93</td>
<td>0.92</td>
<td>0.91</td>
</tr>
<tr>
<td>Arm and wrist</td>
<td>0.95</td>
<td>0.95</td>
<td>0.94</td>
<td>0.93</td>
<td>0.92</td>
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<td>0.89</td>
<td>0.89</td>
<td>0.88</td>
<td>0.86</td>
</tr>
</tbody>
</table>
3.4.3 Vitamin K1

Effects on BMD

The meta-analyses of four homogenous trials, including three vitamin K1 trials (60;61;219) and the Binkley trial (the vitamin K1 and control arms) (63), were done in 1011 women (60;61;63;219). Vitamin K1 slightly decreased the mean BMD at the lumbar spine by 0.18%; however, high uncertainty was present around this and the estimate of future trials (Figure 3.5a). In the influence analysis, the results were similar after omitting the Binkley trial (63) (the pooled MD changed from -0.18% [95% CI:-0.60 to 0.30, I²=4%] to 0.02% [95% CI:-0.50 to 0.50, I²=0%]). The probabilities of showing a 1% increase in BMD were small in current and future trials (≤11%) (Table 3.2).

Vitamin K1 slightly increased the mean BMD at the femoral neck by 0.70% (4 trials (60;61;214;219): 872 women) and the total hip by 0.09%, (3 trials (60;63;219): 744 women) (Figures 3.5b and 3.5c). These changes in BMDs were not statistically significant. Also, the mean percent changes in BMD in future trials were highly uncertain. We found a 62% probability of showing a 1% increase in BMD at the femoral neck in current trials, and a corresponding probability of 56% in a future trial (Table 3.2). In contrast, the probabilities of 1% increase in BMD at the total hip were equal to or less than 2% in current and future trials. In meta-regression models, the effect of vitamin K1 on BMD at the lumbar spine (or any other site) did not depend on the dose of vitamin K1 or the risk of bias (regression slopes: dose (MD, %): -0.58%, 95%CrI:-2.03 to 0.83; and for bias (MD, %): -0.16%, 95% CrI: -1.66 to 1.40) (Figure 3.3).

A 2-year double-blind placebo-controlled trial by Bolton-Smith et al (62) was not included in the quantitative synthesis as it reported absolute changes in BMD (mg/cm2) at various skeletal sites. Two-hundred forty-four healthy Scottish women age ≥ 60 were randomized to vitamin K1, vitamin K1 plus vitamin D and calcium, vitamin D and calcium alone or placebo. No significant differences between the intervention groups at any bone site were found. Only significant bone gain from baseline was shown at the ultradistal radius within a group of women supplemented with the K vitamins, vitamin D and calcium (6.2 mg/cm2, 95%CI: 2.6 to 9.8).
Effects on fractures

The effect of vitamin K1 on the risk of fractures is uncertain as only one trial in 440 Caucasian women with osteopenia reported reductions of all clinical fractures. The confidence interval surrounding the mean treatment effect excluded one but was wide (hazard ratio [HR]:0.45, 95 CI%:0.20 to 0.98) (60).
Figure 3.5a. Forest plot on mean percent changes in BMD at the lumbar spine – vitamin K1 vs. control: Bayesian and classical random-effects meta-analyses. CrI denotes credible interval and CI denotes confidence interval. Bayesian mean percent differences in BMD (Bayesian MD) for each trial are represented by the black circles; the black solid lines through the circles are 95%CrIs. Classical MDs for each trial are represented by the grey circles; the grey dashed lines through the circles are 95%CIs. The black and the blue squares represent Bayesian pooled MDs for the current and a future trial, with the corresponding 95%CrIs. The best-fitting prior on the between-study variance (according to residual deviance) was used to generate Bayesian pooled MDs in current and new trials. The diamond is the estimated classical pooled MD; the length of the diamond reflects 95%CI around the pooled estimate.
<table>
<thead>
<tr>
<th>Study</th>
<th>Bayesian MD (95% CrI)</th>
<th>Classical MD (95% CI)</th>
<th>% Mean Difference (MD) (95% CrI / 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schaafsma 2002</td>
<td>1.4 (-0.4,3.4)</td>
<td>2.1 (-0.3,4.5)</td>
<td></td>
</tr>
<tr>
<td>Braun 2003</td>
<td>1.2 (-0.1,2.6)</td>
<td>1.5 (0.0,3.0)</td>
<td></td>
</tr>
<tr>
<td>Cheung 2008</td>
<td>0.4 (-0.3,1.1)</td>
<td>0.4 (-0.3,1.1)</td>
<td></td>
</tr>
<tr>
<td>Booth 2008</td>
<td>0.0 (-0.9,0.8)</td>
<td>-0.2 (-1.1,0.7)</td>
<td></td>
</tr>
<tr>
<td>Overall: Current</td>
<td>0.7 (-0.7,2.4)</td>
<td>0.6 (-0.2,1.4)</td>
<td></td>
</tr>
<tr>
<td>Future Study</td>
<td>0.7 (-2.5,4.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3.5b. Forest plot on mean percent changes in BMD at the femoral neck – vitamin K1 vs. control: Bayesian and classical random-effects meta-analyses. CrI denotes credible interval and CI denotes confidence interval. Bayesian mean percent differences in BMD (Bayesian MD) for each trial are represented by the black circles; the black solid lines through the circles are 95%CrIs. Classical MDs for each trial are represented by the grey circles; the grey dashed lines through the circles are 95%CIs. The black and the blue squares represent Bayesian pooled MDs for the current and a future trial, with the corresponding 95%CrIs. The diamond is the estimated classical pooled MD; the length of the diamond reflects 95%CI around the pooled estimate.
<table>
<thead>
<tr>
<th>Study</th>
<th>Bayesian MD (95% CrI)</th>
<th>Classical MD (95% CI)</th>
<th>% Mean Difference (MD) (95% CrI / 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schaafsma 2002</td>
<td>0.1 (-0.6,0.9)</td>
<td>0.4 (-1.8,2.6)</td>
<td></td>
</tr>
<tr>
<td>Cheung 2008</td>
<td>0.1 (-0.3,0.6)</td>
<td>0.2 (-0.4,0.8)</td>
<td></td>
</tr>
<tr>
<td>Binkley 2009</td>
<td>0.1 (-0.5,0.5)</td>
<td>-0.1 (-0.7,0.6)</td>
<td></td>
</tr>
<tr>
<td>Overall: Current</td>
<td>0.1 (-0.5,0.7)</td>
<td>0.1 (-0.3,0.5)</td>
<td></td>
</tr>
<tr>
<td>Future Study</td>
<td>0.1 (-0.8,1.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3.5c.  Forest plot on mean percent changes in BMD at the total hip – vitamin K1 vs. control: Bayesian and classical random-effects meta-analyses. CrI denotes credible interval and CI denotes confidence interval. Bayesian mean percent differences in BMD (Bayesian MD) for each trial are represented by the black circles; the black solid lines through the circles are 95%CrIs. Classical MDs for each trial are represented by the grey circles; the grey dashed lines through the cirlcles are 95%CIs. The black and the blue squares represent Bayesian pooled MDs for the current and a future trial, with the corresponding 95%Crls. The diamond is the estimated classical pooled MD; the length of the diamond reflects 95%CI around the pooled estimate.
3.4.4 Sensitivity to priors on the between-study variance

As proposed in the literature (138;141;210), we examined sensitivity of the Bayesian meta-analytic outputs to the choice of eight priors on between-study variance. The residual deviance (RD) was used as the criterion for model fit; the best fitting prior was the one with the lowest value of RD (142). The reference meta-analyses used the best fitting prior on between-study variance to estimate the Bayesian posteriors related to the treatment effect in current and future trials. In Bayesian meta-analysis on the effect of vitamin K2 on BMD, the best fitting prior was uniform on between-study variance ($\tau^2 \sim U(0,3)$) for the analysis on lumbar spine BMD, while the DuMouchel prior on between-study standard deviation was the best for the analyses on femoral neck, total hip and distal radius BMDs. In Bayesian meta-analysis on the effect of vitamin K1 on BMD, the best fitting prior was half-normal on between-study variance for the analysis on lumbar spine BMD, uniform on between-study variance ($\tau^2 \sim U(0,3)$) for the analysis on femoral neck BMD, and the DuMouchel prior on between-study standard deviation for the analysis on total hip BMD. In Bayesian meta-analyses on all clinical, non-vertebral and vertebral fractures, the best fitting prior was uniform on between-study variance ($\tau^2 \sim U(0,3)$).

In sensitivity analysis, the outputs of the vitamin K2 models for the lumbar spine and distal radius BMDs but not those for the femoral neck and total hip BMDs were sensitive to the choice of this prior. For example, the posteriors of MD in BMD at the lumbar spine and distal radius became inconclusive if we specified inverse gamma on variance, uniform on standard deviation or the half-normal priors on variance or standard deviation (Figure 3.6). However, the predictive distributions remained similar and uncertain. The outputs of the fracture models and all models on vitamin K1 remained robust to the changes of the priors on between-study variance.
3.4.5 Publication bias

No evidence of publication bias was found for vitamin K2 and vitamin K1 trials reporting BMD (Figures 3.7-3.8). For the vitamin K2 studies reporting all fractures, funnel plot asymmetry was present, suggesting the small study effect (intercept: -2.9, p=0.04) (Figure 3.9). Also, after imputing missing trials by the trim and fill method, the population OR changed from 0.66 (95% CI: 0.43 to 1.03 in the reference analysis) to 0.87 (95% CI: 0.56 to 1.39) and remained statistically non-significant (Figure 3.9).
Figure 3.7. Funnel plots (the trim and fill method): The effect of vitamin K2 on BMD at the lumbar spine, femoral neck and total hip. BMD denotes bone mineral density, LS, FN and TH denote the lumbar spine, femoral neck and total hip skeletal sites.
FIGURE 3.8. Funnel plots (the trim and fill method): The effect of vitamin K1 on BMD at the lumbar spine, femoral neck and total hip. BMD denotes bone mineral density, LS, FN and TH denote the lumbar spine, femoral neck and total hip skeletal sites.
Figure 3.9. Funnel plot (the trim and fill method) and Egger’s linear regression test: the effect of vitamin K2 on all fractures.
3.5 Discussion

3.5.1 Principal findings

Vitamin K2

Based on our systematic review including Bayesian and classical meta-analyses of the 10 trials in postmenopausal women, vitamin K2 had a discordant effect between different BMD skeletal sites, with a positive effect on the lumbar spine and distal radius but no effect on the femoral neck and total hip. The positive effect of vitamin K2 at the lumbar spine was based on the meta-analyses of eight trials in 1332 women. Vitamin K2 improved the mean BMD at the lumbar spine by 1.2% (over 1-3 years), with a 88% probability of showing a 1% increase in BMD in current trials, and with a 67% probability of showing a clinical benefit in future trials. The use of vitamin K over 12 months was not associated with a statistically significant increase in BMD at the lumbar spine (Figure 3.3). However, several subgroup analyses showed statistically significant increases in BMD and greater probabilities of benefits in women who were older, Asian and osteoporotic, those who were taking a high daily dose of 45mg and were the participants of open-label trials.

All vitamin K2 fracture trials were done in older Asian osteoporotic women. The pooled effect suggested some but uncertain benefits of vitamin K2 on fractures. The chances of finding OR of 0.80 in both current and future studies were moderately high (≥ 75% and ≥ 62%, respectively). A probability of 75% indicates the odds of 3 to 1 in favor of benefit (75:25), and a probability of 60% indicates the odds of 1.5 to 1 in favor of benefit. In meta-regression models, the relationship between baseline fracture rates and the effect of vitamin K2 on fractures was insignificant; but, women with baseline fracture rates greater than 13% possibly benefited more from the treatment. The influence of a 3-year open-label trial by Inoue et al (65) was considerable. This phase IV trial was the largest of all fracture trials including about 3000 older women without fractures and 1400 older women with baseline fractures. Once its data were included in the analysis, the anti-fracture effect of vitamin K2 decreased around twofold and became uncertain (without the Inoue trial: population OR=0.34 [95%CI: 0.20 to 0.57]; with the Inoue trial: population OR=0.66 [95%CI: 0.43 to 1.03])

Our results need to be interpreted with caution because several sources of bias are present in the vitamin K2 meta-analyses. First, most vitamin K2 trials were associated with high risk of bias. Second, the meta-analyses were associated with large between-study heterogeneity; due to large
between-study heterogeneity the predictions of the true mean treatment effects were uncertain as depicted by wide 95% prediction intervals that overlapped zero or one (142). Next, three issues affect validity of the vitamin K2 meta-analysis on fractures: publication bias, small study bias and a small number of pooled studies (152). Lastly, since there was no well-designed trial using high-dose vitamin K2 in Caucasian women at high risk of fractures, a controversy around the anti-fracture effect of vitamin K2 on fractures in this population persists.

**Vitamin K1**

Based on current evidence including four homogeneous trials in Caucasian non-osteoporotic women, vitamin K1 in a daily dose ranging between 0.8-5mg had no effect on the mean percent change at any BMD site. There is large uncertainty around the vitamin K1 effect in future trials, with discrepant probabilities of 1% increase in BMD between the skeletal sites (≥ 56% for the femoral neck and <10% for the lumbar spine or the total hip). Only one trial examined and showed a positive effect of vitamin K1 on fractures (60).

**3.5.2 Relation to other studies**

Three systematic reviews with meta-analyses (42;56;57) and several narrative reviews (15;17;20;223) have been published. The first systematic review published in 2006 by Cockayne et al (56), evaluated 13 trials comparing vitamin K1 and vitamin K2 to control treatments in mixed study populations; seven of these trials examined the effect on fractures and were pooled. In this classical meta-analysis, vitamin K2 was shown to be highly protective of bone loss and fractures particularly in Japanese patients (e.g., vertebral fractures: OR=0.40, 95%CI: 0.25-0.65; and, all non-vertebral fractures: OR=0.19, 95%CI: 0.11-0.35). This review was updated in 2010 and in addition to BMD, bone turnover markers were assessed (presented as an abstract) (224). The updated meta-analysis showed a significant effect of vitamin K1 on reducing undercarboxylated osteocalcin (ucOC), which is considered an independent risk factor for osteoporotic fractures; they also showed no significant effect on BMD at any site. Supplementation with vitamin K2 also significantly reduced ucOC, but in contrast, vitamin K2 significantly increased BMD (combined sites). The authors suggested that vitamin K may be beneficial for bone health as it reduced ucOC (224).

Compared to these systematic reviews (56;224) that included patients with primary or secondary causes of osteoporosis, patients with Alzheimer’s disease or stroke and healthy pre- and
postmenopausal women, our study included trials with postmenopausal women with osteopenia or osteoporosis; it also included a number of new RCTs published since 2005. We found a small effect of vitamin K2: a mean BMD at the lumbar spine increased by 1.2% (95% CrI: 0.00 to 2.53) over one to three years, while there was no effect on BMD at the femoral neck and the total hip. The future treatment effects on BMD were inconclusive. Our study also included all published fracture data until 2012. Compared to the review by Cockayne et al (56), it resulted in smaller mean reductions of odds of all clinical, vertebral and non-vertebral fractures that were also associated with large uncertainty.

Another meta-analysis published in 2009 examined the effect of vitamin K2 on fracture reduction in patients with Alzheimer’s and Parkinson’s diseases or stroke (42). As in the previous meta-analysis by Cockayne et al (56), this analysis of 3 trials in older Japanese patients with neurological diseases showed fracture risk reductions of 86-87% with 45 mg of vitamin K2 daily (42). The authors partially explained an extremely large efficacy of vitamin K2 by malnutrition present in neurological patients, as determined by the low vitamin K and vitamin D serum levels. However, they postulated that the anabolic and potentially anti-resorptive effects of vitamin K2 on bone go beyond a physiological nutrition role or a role in coagulation (17;20;42). Thus, vitamin K2, as a cofactor of γ-carboxylase, ensures functioning of bone protein osteocalcin (38-40), and as a transcriptional regulator of bone-specific genes, ensures the expression of osteoblastic markers (42;43). As an inhibitor of the nuclear factor kappa B, vitamin K2 modulates the expression of interleukin-6 and osteoprotegerin, and consequently, influences bone turnover (20;44;45). Also as an inhibitor of prostaglandin E2, it hinders bone resorption (42;46;47). Through these anabolic and anti-resorptive actions, vitamin K2 possibly improves bone quality and strength even without increasing BMD (17;42). Nevertheless, because of methodological limitations of the trials, the authors also suggested the need for another larger RCT to corroborate the anti-fracture effect of vitamin K2 in Japanese populations with neurological diseases (42).

Lastly, a 2011 meta-analysis by Fang et al compiled together vitamin K2 and vitamin K1 trials in all populations to examine their combined effect on BMD (57). Vitamin K treatment ranging from six to 36 months resulted in a 1.3% increase in BMD at the lumbar spine and no change at the femoral neck. In our Bayesian meta-regression model that included only postmenopausal women and accounted for the duration of treatment, we found a 1.5% mean increase in BMD at the lumbar spine in women treated with vitamin K2 for at least two years (Figure 3.3). This alleviation of bone loss at the lumbar spine can be comparable to the effect of vitamin D and calcium on BMD at the femoral neck in older
Caucasian women (205). A biannual increase of at least 1% in BMD at any major skeletal site could be considered a clinically meaningful effect of non-pharmacologic bone therapies.

3.5.3 Strengths and limitations

We performed a thorough systematic review guided by the currently accepted recommendations for assessing and synthesizing the evidence (197;199). We comprehensively searched the literature to identify eligible English and non-English studies. We used a recommended Cochrane tool for the assessment of bias within a study. Also, two reviewers independently evaluated and extracted the data, with a third reviewer to settle the differences. Our study employed univariate Bayesian random-effects methods to examine the efficacies and the probabilities of benefits of the K vitamins on BMD or fractures in current and future studies.

However, our study has some limitations. First, it is limited by the relatively low quality of some of the primary data, and therefore, its findings should be interpreted with caution. Second, due to variations in the reporting of the BMD results, our meta-analyses pooled the mean percent changes in BMD (as the most commonly reported BMD outcome). Nevertheless, as suggested in the PRISMA guidelines for reporting and conducting systematic reviews (197), we qualitatively synthesized a few studies (62;64;215;221) that reported only areal BMD or BMD T-scores. It is worth noting that the risk of bias of the qualitatively examined trials was either high (64;215;221) or unclear (62) (Appendix: Table A3.2). Since no information about the correlation between the baseline and follow-up data was provided in these studies, approximations of the mean percent changes were deemed inappropriate. Additionally, inclusions of these studies would not considerably change the conclusions of our meta-analyses. For example, the inclusion of the Yasui and Mochanis vitamin K2 trials (64;221) would add a small number of women to the analysis (43 to vitamin K2 group and 56 to placebo group). Both trials showed only small increases in areal BMD (g/cm2) at the lumbar spine, and their addition most likely would not change our conclusions. The inclusion of the trial by Hirao et al (215) that reported the BMD outcome in T-score units may be inappropriate as this study compared vitamin K2 to alendronate and did not have a placebo or any other control arm. We a priori specified to pool the data of control groups using non-pharmacological therapies (vitamin D or calcium) or placebo because of the variety of control groups found in the vitamin K2 trials. Regarding vitamin K1, adding the data of the Bolton-Smith trial (62) to the analysis would increase a sample by 110 women (56 - placebo and 54 - vitamin K1), for the femoral neck skeletal site only (the lumbar spine BMD was not examined). Transformations and imputations of the data would be more challenging, as the mean
changes in areal BMD (mg/cm2) and their 95% CIs were presented in tables, but the baseline and follow-up areal BMD values were presented in graphs. Additionally, the mean changes in the placebo and vitamin K1 only groups were associated with wide 95% CIs that overlapped zero; thus, most likely adding this trial to our univariate meta-analyses would not change the conclusion as to a small but also an uncertain effect of vitamin K1 on BMD at the femoral neck. Finally, a few vitamin K2 trials assessing BMD at the lumbar spine had multiple control arms; in additional analyses, adjusting for multiplicity (Appendix: Table A3.2), the increase in BMD changed from 1.2% (95%CrI: 0.0 to 2.5) to 0.8% (95%CrI: -0.3 to 1.9), but the probabilities of benefits remained $\geq 59\%$ and $\geq 70\%$ in current and future trials.

3.5.4 Conclusions

The K vitamins had small or nil effects on BMD at various skeletal sites. Vitamin K2 benefited BMD at the lumbar spine, femoral neck and distal radius with a probability greater than 50%; vitamin K1 only benefited BMD at the femoral neck. The probabilities of any benefit on fractures were greater than 70% in current and future trials. However, the current and future efficacy estimates were associated with large uncertainties and were inconclusive. Our evidence synthesis confirms a gap in knowledge regarding the effect of vitamin K on fractures. Based on our analysis, we do not support use of the K vitamins for the prevention and treatment of osteoporosis in Caucasian postmenopausal women until their beneficial effects on fractures are demonstrated in future studies.

3.6 Acknowledgements

We thank Ms. Zoe Agnidis (ZA) for assessing the risk of bias of eligible trials and extracting the outcome data. We thank Mr. Panos Lambiris, a UHN hospital librarian, for helping us develop search strategies for this review. The preliminary results of this study were presented at the 2011 ASBMR meeting, Sep 16-21 2011, San Diego, California, USA.
Chapter 4
Exploring uncertainties in the treatment effects of the K vitamins on BMD and fractures in Bayesian bivariate meta-analysis

4. Study 3

4.1 Abstract

Purpose: Systematic reviews that do not account for correlated outcomes may lead to biased estimates of treatment effects. We examined uncertainty in the estimates of vitamin K treatment effects on two correlated bone outcomes in Bayesian bivariate meta-analysis and explored how these results would alter the results of our published cost-effectiveness analysis.

Methods: We used data from a systematic review of 14 vitamin K trials that reported either BMD or fractures or both endpoints. We identified three trials reporting both BMD and fracture outcomes. We used Bayesian hierarchical bivariate random-effects meta-analysis to sample incomplete data and model simultaneously four pairs of outcomes: lumbar spine BMD and all fractures; lumbar spine BMD and vertebral fractures; femoral neck BMD and non-vertebral fractures; and, vertebral and non-vertebral fractures. We specified non-informative priors on the mean treatment effects and a Wishart prior on the inverse of the between-study variance-covariance matrix. For each outcome, we estimated the population treatment effect in current trials and the prediction of the treatment effect in future trials. The between-study correlations and the probabilities that vitamin K benefited both bone outcomes were calculated. We compared univariate and bivariate random-effects meta-analysis and used the population and future odds ratios as input parameters into a model examining the cost-effectiveness of the K vitamins for preventing fractures in women initially without osteoporosis.

Results: While the pooled estimates of the bivariate and univariate random-effects meta-analyses were similar, the bivariate 95% credible intervals (CrIs) were narrower. The predictive distributions shrank the most. For example, the population and future odds ratios for the effect of vitamin K2 on vertebral fractures and lumbar spine BMD using bivariate methods were 0.81 (95% CrI: 0.5-1.1) and 0.84 (95% CrI: 0.4-1.5); the corresponding univariate estimates were 0.67 (95% CrI: 0.2-1.5) and 1.20 (95% CrI: 0.1-5.2). The probabilities of joint benefit were 89% (vitamin K2) and 12% (vitamin K1) for vertebral fractures and lumbar spine BMD, and 49% (vitamin K2) and 75% (vitamin K1) for non-vertebral...
fractures and femoral neck BMD. Using the results from the univariate analysis, both vitamin K2 and K1 strategies cost less than $50,000/QALY; using future odds ratios from the bivariate analysis, the vitamin K2 strategy cost more than $100,000/QALY and the vitamin K1 strategy was cost-saving.

**Conclusion:** Bivariate random-effects meta-analysis can yield more precise estimates of the treatment effects that can meaningfully change the results of an economic analysis.

**Keywords:** Bayesian, bivariate random-effects meta-analysis, incomplete data, vitamin K, fractures, cost-effectiveness.

### 4.2 Introduction

Evidence synthesis is a methodological approach used to summarize the results of clinical trials. Meta-analysis – a quantitative component of evidence synthesis – is used to evaluate the state of current knowledge, identify a gap in knowledge and consequently inform decisions regarding future research (114-118). It has been previously noted by others that most meta-analyses are conducted as univariate analyses, examining one outcome at a time (123;124), despite the fact that most treatments have effects on more than one outcome (120-123). Within one study, the effect of treatment is often examined separately for several different outcomes (e.g., disease-free survival and overall survival, BMD and fractures or CD4 cell count and development of AIDS or death), or across several comparison groups or several time points (120;125). The multiple outcomes assessed for each subject within a trial are often correlated; consequently, the measured treatment effects are correlated and conducting several separate univariate meta-analyses ignores this dependence and increases the risk of Type I error across the entire set of meta-analyses (125).

To allow a joint synthesis of treatment effects on multiple outcomes and account for their correlation within a study and between studies, multivariate meta-analysis should be conducted (122;126-132). The simplest and the most frequently used type of multivariate meta-analysis is bivariate meta-analysis that simultaneously models treatment effects measured on two correlated outcomes (127;129;132;133). Bivariate meta-analysis can be done by pooling the trial data at individual-level or at aggregate level. If individual-level data are available, correlations between the outcomes can be estimated; however, in standard meta-analyses using aggregate data, correlations between the outcomes within a trial (i.e., within-study correlations) cannot be estimated. Nonetheless, when treatment effects measured on two
outcomes are correlated at the individual level, it is reasonable to assume that the summary treatment
effect estimates will also tend to be correlated (225). Additionally, within-study correlations need to
be distinguished from the between-study correlation that is estimated in bivariate meta-analysis. An
estimate of the between-study correlation shows a direction of changes of treatment effects across all
studies: for example, entire studies with a large treatment effect on one outcome may also have large
treatment effects on other outcomes.

In addition to an approximation of the between-study correlation, bivariate meta-analysis may provide
several other advantages over univariate meta-analysis. First, bivariate random-effects meta-analysis
(BRMA) can be used to yield a prediction of the treatment effect in a future study (80). While
predictions can be obtained from univariate random-effects meta-analysis (URMA), BRMA has been
shown to generate a more precise prediction estimate of the treatment effect due to the process of
“borrowing strength” (122;126;127;129;131;134). Second, studies often measure the effect of
treatment using surrogate outcomes instead of the most important outcomes (e.g., BMD vs. fractures)
(124). Given known correlations between a surrogate outcome and the most important outcome and
through “borrowing strength” across studies and across the outcomes (127-129;134), BRMA can make
use of all available data; it can be used to forecast the effect of treatment on the unmeasured but often
more important outcome. Another unique advantage of BRMA is to estimate the probability of joint
benefit of the treatment on both outcomes – information that can be quite relevant to clinicians. Lastly,
the estimates of BRMA can be used in economic evaluations (99;102;114;226;227).

However, BRMA is associated with some important challenges shown in simulation studies using both
classical or Bayesian hierarchical models (126-129;132;134;228). First, as previously mentioned,
BRMA models require information on the within-study correlations for each included trial – data that
are rarely reported in the original studies (127-129;132;134;228). In this situation, Bayesian
hierarchical BRMA has some advantage over the classical approach because a prior distribution on
unknown within-study correlation can be specified (129). Next, most BRMA models include studies
that report summary statistics for only one endpoint (124). These missing treatment effects may be
measured but not reported (outcome reporting bias), or may be truly missing (i.e., not measured). In
any case, assuming missingness at random (MAR) is the most commonly used approach. Under a
MAR assumption, within-study correlations are used to generate an overall estimate of bivariate
treatment effect (128). Third, modeling becomes more complex if BRMA is used to synthesize
incomplete data of different types of outcomes (e.g., binary and continuous). Missing data related to
variances, means and numbers of events in treatment and control groups need to be imputed to obtain the summary statistics. In this case, Bayesian hierarchical BRMA is especially advantageous since it can sample incomplete data through Markov Chain Monte Carlo (MCMC) simulations (122;128;129). Despite these advantages, little empirical research has examined the properties of Bayesian BRMA in a small set of pooled trials (122;129).

To increase our understanding of the potential and challenges of Bayesian BRMA, we conducted an empirical study that combined the summary treatment estimates of binary (fracture) and continuous (BMD) outcomes. These outcomes were previously analyzed as independent in several Bayesian URMAs, in which the estimates of treatment effect in current and particularly in future studies were inconclusive (see Chapter 3). Since the vitamin K univariate meta-analyses included a relatively small number of vitamin K2 and vitamin K1 trials, we were also able to explore the properties of Bayesian BRMAs that were small in size. Based on previous research (126-129;132;134;228), we hypothesized that our bivariate meta-analyses would lead to more precise pooled estimates. The specific aims of this study were to evaluate the simultaneous effects of vitamin K2 or vitamin K1 on BMD and fractures at various skeletal sites, to predict their treatment effects in future trials and to obtain the probabilities of joint benefit on two outcomes. We also aimed to estimate the between-study correlation to determine an overall direction of the vitamin K effect across all trials. Finally, we explored whether the bivariate treatment effect estimates would alter the results of our cost-effectiveness analysis (196) (presented in chapter 2).

4.3 Methods

4.3.1 Data

Pairs of treatment effects on BMD and fracture outcomes were jointly modeled as bivariate in hierarchical Bayesian BRMA. The BMD components of the bivariate outcomes were the mean differences in BMD at the lumbar spine or the femoral neck. These two skeletal sites were chosen as they are most often used for fracture risk assessments (13;14;229). The BRMA analyses included trials that reported BMD (only those that measured mean percent changes in BMD) or fractures or both. The fracture components of the bivariate treatment effects included all reported fractures, vertebral and non-vertebral fractures. A total of eight BRMAs examined the following combinations of outcome pairs separately in vitamin K2 and vitamin K1: 1) BMD at the lumbar spine and all
fractures; 2) BMD at the lumbar spine and vertebral fractures; 3) BMD at the femoral neck and non-vertebral fractures; and 4) vertebral and non-vertebral fractures. Our study was approved by the Research Ethics Boards of University Health Network and the University of Toronto.

When summary estimates were reported for both endpoints, we defined the pairs of treatment effects as “complete”; otherwise, when one summary estimate was missing, we defined the pairs of treatment effects as “incomplete”. Table 4.1a presents three possible cases of BRMA: one includes the pairs of completely reported treatment effects, while the other two cases model incompletely reported bivariate treatment effects. As the pairs of treatment effects on binary and continuous outcomes were modeled together, we used natural log-transformations of odds (logit transformations) to model means and proportions on the same linear scale (230).
Table 4.1a. Estimation of parameters in BRMA: Completely and incompletely reported treatment effect on two different types of outcomes (BMD and fractures)

<table>
<thead>
<tr>
<th>BRMA Case</th>
<th>Trial Outcomes Reported</th>
<th>Assumed, imputed or sampled</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRAC and BMD</td>
<td>Y1[i] Log-odds ratio</td>
<td>Y2[i] Mean difference (MD)</td>
</tr>
<tr>
<td></td>
<td>Reported</td>
<td>Reported</td>
</tr>
<tr>
<td>FRACTURE only</td>
<td>Reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>INCOMPLETELY reported estimates: BMD only</td>
<td>Not reported</td>
<td>Reported</td>
</tr>
</tbody>
</table>
4.3.2 Modeling completely reported treatment effects on two binary outcomes: BRMA on vertebral and non-vertebral fractures

We modeled changes in the mean log-odds ratios of vertebral and non-vertebral fractures using a general framework for BRMA (128;228). A pair consisting of two correlated variables denoted as $Y_1$ and $Y_2$ was modeled using a bivariate normal distribution in a random-effects model outlined below:

$$
\begin{align*}
\begin{pmatrix}
Y_{1i} \\
Y_{2i}
\end{pmatrix}
&\sim N\left(
\begin{pmatrix}
\mu_{1i} \\
\mu_{2i}
\end{pmatrix},
\delta_i
\right) \\
\delta_i &= \begin{pmatrix}
\sigma_1^2 \\
\rho_1 \sigma_1 \sigma_2
\end{pmatrix}
\begin{pmatrix}
\rho_1 \sigma_1 \sigma_2 \\
\sigma_2^2
\end{pmatrix}
\end{align*}
\tag{1a}
$$

$$
\begin{align*}
\begin{pmatrix}
\mu_{1i} \\
\mu_{2i}
\end{pmatrix}
&\sim N\left(
\begin{pmatrix}
d_1 \\
d_2
\end{pmatrix},
\Omega
\right) \\
\Omega &= \begin{pmatrix}
\tau_1^2 \\
\rho_b \tau_1 \tau_2 \\
\rho_b \tau_1 \tau_2 \\
\tau_2^2
\end{pmatrix}
\end{align*}
\tag{1b}
$$

where $Y_{1i}$ and $Y_{2i}$ denote estimates of the mean log-odds ratios reported on two fracture outcomes in trial $i$, where $i$ ranges from 1 to the total number of trials $I$. Assuming a random-effects model, $Y_{1i}$ and $Y_{2i}$ are sampled from bivariate normal distributions with different true mean values $\mu_{1i}$ and $\mu_{2i}$ and trial-specific within-study covariance matrices $\delta_i$. The underlying true values $\mu_{1i}$ and $\mu_{2i}$ are further sampled from a multivariate normal distribution with the two-component mean vector $(d_1, d_2)$ and the between-study variance-covariance matrix $\Omega$. The correlation between the study-specific treatment effects ($\mu_{1i}$ and $\mu_{2i}$) on the measured outcomes, referred to as between-study correlation, is estimated in BRMA and is denoted as $\rho_b$. This correlation and the between-study variance of each treatment effect $(\tau_1^2, \tau_2^2)$ are estimated from the variance-covariance matrix ($\Omega$).

4.3.3 Modeling incompletely reported treatment effects on two outcomes: BRMA on BMD and fractures

When modeling the pairs with incomplete outcome reporting, the analyst needs to recognize which type of outcome is missing (Table 4.1a), and which one is the easiest to impute. Simple imputations (e.g., pooled standard deviations) or Markov Chain Monte Carlo (MCMC) simulations can be used to impute or generate incomplete data, given MAR (i.e., missing outcomes were not dependent on the values of unobserved data) (122;128;129).
4.3.4 Incompletely reported treatment effects on a continuous outcome

When treatment effects on continuous outcomes (i.e., mean differences [MD] in BMDs) were missing and treatment effects on binary endpoints (i.e., log-ORs on fractures) were complete (Table 4.1a), we determined sample sizes, mean treatment effects and their variances for the missing MDs using the following assumptions and simple imputations. We assumed that if both endpoints had been measured, then the trials with incomplete MDs on BMD outcomes would have had the same number of subjects in the control and treatment groups for BMD as they had for fracture outcomes. We imputed the missing standard deviations (treatment and control groups) using pooled standard deviations from a meta-analysis of the variance data of the trials with complete BMD outcomes. Each missing MD in BMD in trial \( i \) was sampled from the bivariate normal distribution in equation 1a, conditional on the logOR in that trial \( i \) (please see section 4.3.7).

4.3.5 Incompletely reported treatment effects on a binary outcome

When only binary outcomes were missing, we needed to estimate missing information for the samples of treatment and control groups and the numbers of events in each group. The within-study variance \( \sigma_i^2 \) is a function of the actual numbers with and without fracture in each study arm, so we had to generate this data. We used Bayesian hierarchical modeling to sample incomplete data through MCMC simulations (122;128;129). This process comprised several steps:

First, the log-odds in the control groups (denoted as \( \alpha_i \)) were based on a normal informative prior as shown in equation 2. This prior was derived from a meta-analysis of log-odds in the control groups of four vitamin K2 trials that reported fractures (65;168;170;171). It had the mean (log-odds) of -1.2 and variance of 0.14; this corresponds to the baseline odds of 0.30 (95% CI: 0.14-0.62):

\[
\alpha_i \sim N(-1.2, 0.14); \quad \logit(p_{ci}) = \alpha_i
\]

Second, the proportions of subjects in the treatment groups (\( p_{ti} \)) were estimated using logistic regression:

\[
\logit(p_{ti}) = \alpha_i + \mu_{ti} \quad i=1,2,3…I
\]

where \( \alpha_i \) is the log-odds in the control group of trial \( i \) and \( \mu_{ti} \) is the log-odds ratio for treatment in trial \( i \); \( \mu_{ti} \) is sampled from its posterior distribution conditional on the vitamin K effect on BMD in this trial. Note that \( \mu_{ti} \), the log-odds ratio for trial \( i \), is the first component of the bivariate outcome in equation 1a.
Next, the probabilities of events in the treatment and control groups (denoted as $p_t$ and $p_c$) were computed from observed trial sample sizes (denoted as $n_t$ and $n_c$) reported for the BMD outcomes. Table 4.1b shows an example of one dataset used in the analysis. The unobserved outcomes in the treatment and control groups for trial $i$ (denoted as $r_t$ and $r_c$) were generated from binomial distributions (equations 4 and 5):

$$rt_i \sim \text{Binom}(p_t, n_t) \quad i=1,2,3\ldots I;$$

$$rc_i \sim \text{Binom}(p_c, n_c) \quad i=1,2,3\ldots I;$$

Lastly, once the samples for each group were generated, we approximated the standard deviation of the log-odds ratio (denoted as $sd\log\text{OR}$) for each trial $i$ as following:

$$sd\log\text{OR} = \sqrt{\frac{1}{rc + 0.5} + \frac{1}{nc - rc + 0.5} + \frac{1}{rt + 0.5} + \frac{1}{nt - rt + 0.5}}$$

Table 4.1b. An example of the dataset with few trials that completely reported treatment effects on both BMD and fracture outcomes

<table>
<thead>
<tr>
<th>N</th>
<th>nt</th>
<th>nc</th>
<th>rt</th>
<th>rc</th>
<th>logOR</th>
<th>sdLogOR</th>
<th>MD</th>
<th>sdMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1372</td>
<td>1381</td>
<td>112</td>
<td>107</td>
<td>0.056</td>
<td>0.140</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>627</td>
<td>635</td>
<td>175</td>
<td>181</td>
<td>-0.029</td>
<td>0.125</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>66</td>
<td>9</td>
<td>20</td>
<td>-0.981</td>
<td>0.439</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>24</td>
<td>2</td>
<td>6</td>
<td>-1.106</td>
<td>0.809</td>
<td>0.520</td>
<td>0.819</td>
</tr>
<tr>
<td>5</td>
<td>91</td>
<td>99</td>
<td>14</td>
<td>35</td>
<td>-1.078</td>
<td>0.354</td>
<td>2.700</td>
<td>1.425</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>33</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.605</td>
<td>1.076</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>17</td>
<td>19</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.100</td>
<td>0.699</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>161</td>
<td>164</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.220</td>
<td>0.531</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>167</td>
<td>167</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.050</td>
<td>0.386</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.920</td>
<td>0.448</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>126</td>
<td>129</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.865</td>
<td>0.472</td>
<td></td>
</tr>
</tbody>
</table>

N = trial $i$; nt and nc denote the total numbers of patients in the treatment and control arms of trial $i$; rt and rc denote the numbers of patients with the outcomes in the treatment and control groups of trial $i$; logOR and sdLogOR denote log-odds ratio and its standard deviation; MD and sdMD denote mean difference in BMD and its standard deviation; dash (-) denotes missing values.
4.3.6 Datasets where no study reports both types of treatment effects

BRMA can also include the scenario when none of the studies had complete reporting of the treatment effects (Table 4.1c). The purpose of this BRMA was to forecast unmeasured treatment effects of vitamin K2 on BMD and fracture outcomes by utilizing assumed within-study correlation. The between-study correlation had to be estimated from a prior. This type of BRMA could serve to reduce outcome reporting bias (122;153), as it could happen that some of the trials did measure treatment effects on both outcomes but selectively analyzed or fully reported statistically significant outcomes (231).

Table 4.1c. An example of the dataset where no trial completely reported treatment effects on both outcomes

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>nt</th>
<th>nc</th>
<th>rt</th>
<th>rc</th>
<th>logOR</th>
<th>sdLogOR</th>
<th>MD</th>
<th>sdMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1372</td>
<td>1381</td>
<td>36</td>
<td>36</td>
<td>0.0067</td>
<td>0.237</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>627</td>
<td>635</td>
<td>24</td>
<td>29</td>
<td>0.1807</td>
<td>0.279</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>66</td>
<td>66</td>
<td>0</td>
<td>3</td>
<td>-1.992</td>
<td>1.522</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>23</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>0.0416</td>
<td>2.021</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>91</td>
<td>99</td>
<td>1</td>
<td>5</td>
<td>-1.256</td>
<td>0.933</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>161</td>
<td>167</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.069</td>
<td>0.538</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>164</td>
<td>167</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.160</td>
<td>0.271</td>
</tr>
</tbody>
</table>

N = trial i; nt and nc denote the total numbers of patients in the treatment and control arms of trial i; rt and rc denote the numbers of patients with the outcomes in the treatment and control groups of trial i; logOR and sdLogOR denote log-odds ratio and its standard deviation; MD and sdMD denote mean difference in BMD and its standard deviation; dash (-) denotes missing values.

4.3.7 Regression-based BRMA of observed and generated treatment effects on two outcomes

Once all missing data were estimated, both sampled and observed outcome pairs were pooled within BRMA using the linear regression representation of the bivariate normal distribution, assuming approximate normal likelihood (126;129-131) and random-effects (80). The modeling was done in several steps to generate the parameters of the first part of a general BRMA framework previously denoted as equation 1a.

First, for each trial i, log-odds ratios denoted as \( Y_{1i} \) were assumed to be sampled from a normal distribution with different underlying true values for the mean log-odds ratio (denoted as \( \mu_{1i} \)) and variance (denoted as \( \sigma^2_{1i} \)):
\[
Y_{1i} \sim N(\mu_{1i}, \sigma^2_{1i}), \quad i = 1, 2, 3 \ldots I \tag{7}
\]

For trial \(i\), given \(Y_{1i}\), mean differences \(Y_{2i}\) were assumed to be sampled from a normal distribution with conditional mean:

\[
E(Y_{2i} | Y_{1i}) = \mu_{2i} + \rho_{wi} \sigma_{2i}/\sigma_{1i} (Y_{1i} - \mu_{1i}) \tag{8}
\]

and conditional variance \((\sigma^2_{2i}(1-\rho^2_{wi}))\), where as above in equation 1a, \(\rho_{wi}\) is the trial-specific within-study correlation.

Taken together, the unconditional normal distribution for \(Y_{1i}\) in (7) and the conditional normal distribution for \(Y_{2i}\) in (9) are equivalent to the bivariate distribution for \((Y_{1i}, Y_{2i})\) in equation 1a.

\[
Y_{2i} | Y_{1i} \sim N( \mu_{2i} + \rho_{wi} \sigma_{2i}/\sigma_{1i} (Y_{1i} - \mu_{1i}), \sigma^2_{2i}(1-\rho^2_{wi})) \tag{9}
\]

The two underlying true mean values \(\mu_{1i}\) and \(\mu_{2i}\) were further jointly modeled using a general BRMA framework (see equation 1b) (122;126;128;129;228):

\[
\begin{pmatrix}
\mu_{1i} \\
\mu_{2i}
\end{pmatrix} \sim N\left(\begin{pmatrix} d_1 \\ d_2 \end{pmatrix}, \Omega \right)
\]

\[
\Omega = \begin{pmatrix}
\tau_1^2 & \rho_{B} \tau_1 \tau_2 \\
\rho_{B} \tau_1 \tau_2 & \tau_2^2
\end{pmatrix}
\tag{10}
\]

where \(d_1\) and \(d_2\) denote the population mean treatment effects for the outcomes; \(\Omega\) denotes the between-study variance-covariance matrix which consists of the between-study covariance and the two between-study variances, denoted as \(\tau_1^2\) for the log-odds ratio and \(\tau_2^2\) for the mean difference. The between-study covariance is the product of the between-study correlation and between-study standard deviations: \(\rho_{B} \tau_1 \tau_2\) (134).

### 4.3.8 Main outputs of BRMA

For each BRMA, we obtained the posterior distributions for the following parameters: population mean treatment effects (\(d_1\) the population logOR and \(d_2\), the population mean difference [MD]), predicted true treatment effects in a future trial (\(D_{new 1}\) and \(D_{new 2}\) for future logOR and future MD) between-study variances (\(\tau_1^2\) and \(\tau_2^2\)) and between-study correlation (\(\rho_{B}\)). The 2.5th and 97.5th percentiles of the posterior distribution were used to create a 95% credible interval (95% CrI) for each parameter.
Predictive distributions are important outputs of BRMA. The posterior predictive distributions of the true treatment effect (denoted as $D_{new_1}$, $D_{new_2}$) were sampled from the posteriors of the normal bivariate distribution of the population treatment effects ($d_1$ and $d_2$):

$$
\left( \begin{array}{c} D_{new_1} \\ D_{new_2} \end{array} \right) \sim N\left( \left( \begin{array}{c} d_1 \\ d_2 \end{array} \right), \Omega \right)
$$

$$
\Omega = \begin{pmatrix}
\tau_1^2 & \rho_{\tau_1 \tau_2} \\
\rho_{\tau_1 \tau_2} & \tau_2^2
\end{pmatrix}
$$

The next important outputs of BRMA are probabilities of simultaneous benefit on both outcomes in current and future trials. From the posterior distributions of the population treatment effect ($d_1$ and $d_2$) and the posterior predictive distributions of the treatment effect ($D_{new_1}$ and $D_{new_2}$), we calculated the probabilities of any benefit (clinically meaningful benefit) on both outcomes in current and future trials. As previously justified in chapter 3, clinically meaningful benefits were based on the ranges of treatment effects attained with vitamin D and calcium (204-207). We defined clinically meaningful joint benefit as showing simultaneously MD of 1% and OR of 0.8 in a bivariate BMD-fracture outcome. Similarly, OR of 0.8 for a bivariate fracture outcome was considered clinically meaningful. We made an assumption that a probability of the treatment benefit over 50% on both outcomes indicates an important improvement (135;145).

4.3.9 Prior distributions and assumptions on the within-study and the between-study correlations

To generate posterior distributions for the main outputs of BRMA, we specified non-informative prior distributions on parameters (138;210). As suggested in the literature (232;233), we specified a Wishart prior on the inverse variance-covariance matrix or precision matrix $\Omega^{-1} \sim \text{Wish}(S, t)$; this is a conjugate prior distribution for the precision matrix of multivariate normal distribution. The S parameter is the scale matrix and is the prior mean of the variance-covariance matrix, while the t parameter represents degrees of freedom and is related to the prior variance of $\Omega^{-1}$ around S. In small meta-analyses, t is set to the smallest feasible value (2 or 3) (232). In our reference BRMAs, we specified the Wishart prior using the following values for the S and t parameters

$$
\Omega^{-1} \sim \text{Wish}\left( \begin{pmatrix} 0.09 & 0 \\ 0 & 0.5 \end{pmatrix}, 3 \right)
$$

as they closely represented the estimates of between-study variance generated by the URMAs. In addition to the prior on the variance-covariance matrix, we specified normal non-informative priors on the mean treatment effects ($d_j \sim N(0,0.0001)$, where $j = 1, 2$).
Since data on the within-study correlations ($\rho_{wi}$) were not available from the vitamin K trials, we used data from the literature and an approximate formula to estimate within-study correlations (122). In our BRMAs, we assumed these estimates as known and fixed. We used the log-odds ratios reported in observational studies (that represented the relationship between BMD and fractures within a study) (69;234-237) to approximate the value of within-study correlation coefficient $\rho_{wi}$ using the following formulas (113):

a) Conversion of the log-odds ratio ($\text{LogOddsRatio}$) to the standardized mean difference ($D$):

$$D = \text{LogOddsRatio} \times \frac{\sqrt{3}}{\pi}, \text{ where } \pi = 3.14159$$

b) Conversion of $D$ into the correlation coefficient $\rho_{wi}$:

$$\rho_{wi} = \frac{D}{\sqrt{D^2 + a}}, \text{ where } a \text{ is a correction factor}$$

$$a = \frac{(n_1 + n_2)^2}{n_1n_2}, \text{ where } n_1 \text{ and } n_2 \text{ are the sample sizes in the two groups.}$$

Based on observational studies (69;234-237) that examined the relationship between changes in BMD and changes in odds of fractures, we calculated a small negative within-study correlation of 0.25 between the fracture and BMD effects; our estimate agrees with the estimates reported in a modeling study by Kanis et al (238). We assumed a high positive within-study correlation of 0.80 between effects on two fracture outcomes (162;239-242).

The between-study correlation $\rho_b$, which is unknown and estimated in BRMA, indicates how the underlying true values ($\mu_{1i}$ and $\mu_{2i}$) are related across the combined studies (134). To enhance convergence of the Bayesian BRMA models that included the small numbers of trials with incomplete outcomes, and to enable better estimation of the between-study correlation $\rho_b$, we “borrowed” information on $\rho_b$ from the bisphosphonate literature. This was done through several steps. First, we identified bisphosphonate trials that reported completely both BMD and fracture outcomes using the data of a systematic review by Cheung et al (1995-2005) (243). After updating the search (2005-2011), we found 14 eligible RCTs in 19 500 postmenopausal patients that compared a bisphosphonate (alendronate, cyclic etidronate, risedronate, pamidronate or zolendronic acid) to control (placebo or...
calcium) (176;244-256) (Appendix: Table A4.2). Second, for each trial, we extracted the mean percent changes in BMD at the lumbar spine and the femoral neck and the numbers of all fractures, vertebral and non-vertebral fractures. We calculated the corresponding mean differences and log-odds ratios via Bayesian URMAs. We used these data to approximate the within-study correlation. Based on evidence from the drug trials on bisphosphonates, we calculated the value of -0.175 for the within-study correlations; this value is close to the estimated coefficient of -0.25 from the observational studies (69;234-237). Lastly, assuming the same distribution on the between-study correlation between the bisphosphonate and vitamin K data, we modeled concurrently the effect sizes of the bisphosphonate and vitamin K2 (or vitamin K1) trials.

In addition, we performed BRMAs of the bisphosphonate trials only and obtained the posteriors of the between-study correlation for: 1) BMD at the lumbar spine–vertebral fractures; 2) BMD at the lumbar spine–all fractures; and, 3) BMD at the femoral neck–non-vertebral fractures (Appendix: Tables A4.3). To examine influence of the “borrowing strength” assumption on the estimation of the between-study correlation ($\rho_b$), we compared the posteriors of $\rho_b$ obtained in the BRMAs including the vitamin K and bisphosphonate trials to the posteriors of $\rho_b$ based solely on the bisphosphonate trials.

4.3.10 Sensitivity analyses

We performed three sensitivity analyses to examine our assumptions on the within- and between-study correlations. First, we examined robustness of the parameters of BRMAs to various clinically plausible estimates of the within-study correlation $\rho_{wi}$ (from -0.25 to -0.01 in the BRMAs on BMD-fracture outcomes and from 0.50 to 0.90 in the BRMA on two fracture outcomes) (Appendix: Tables A4.4). In addition, as recommended by Riley et al, we examined the influence of the extreme values of the within-study correlation coefficient on the main outputs of BRMA (128). Next, we explored changes in the estimates of BRMAs after the between-study correlation $\rho_b$ was modeled using the data of vitamin D and calcium trials. To estimate another $\rho_b$, we conducted a search of published vitamin D and calcium reviews (204-207;257;258) and identified three trials reporting both endpoints (BMD at the femoral neck and non-vertebral fractures) (165;259;260) (Appendix: Tables A4.3). Third, we performed a sensitivity analysis to the choice of the mean of a multivariate Wishart prior denoted as $S$ [$\Omega^{-1} \sim \text{Wish}(S, t)$]. For the $S$ parameter, we assumed large and small values of between-study variances as suggested in the literature (138), while the $t$ parameter was kept at the same value (232).
4.3.11 Application to cost-effectiveness analysis

We used the univariate and bivariate population and future ORs for vitamin K2 and vitamin K1 to populate our microsimulation model (196) (chapter 2). In the original model, we used three different vitamin K efficacy estimates (ORs) for hip, vertebral and wrist fractures; in the new models, we replaced the original ORs for hip and wrist fractures with the Bayesian efficacy estimates (ORs) for non-vertebral fractures. We calculated the incremental QALYs and incremental costs, ICERs and population EVPIs (at a threshold of $50,000/QALY) for the vitamin K2 and vitamin K1 strategies (as compared to vitamin D and calcium alone). We examined whether the Bayesian estimates would alter the conclusions of the original cost-effectiveness analysis (CEA). We also graphically presented the probabilities of cost-effectiveness of the vitamin K strategies obtained for each CEA at various willingness-to-pay thresholds using the method of cost-effectiveness acceptability curve (CEAC).

4.3.12 Computations

The Bayesian analyses were done in WinBUGS 1.4.3 (Imperial College and MRC, UK, 2007) (211) and R 2.13.1 (The R Foundation for Statistical Computing, Austria, 2010). They were done to the same standard: we ran three Markov chains starting at dispersed sets of initial values for a total of 300,000 iterations, of which the first 30,000 were discarded. Convergence of the chains was checked by Brooks–Gelman–Rubin (BGR) plots and the Gelman–Rubin statistic (213). The chains were considered to have converged when the Gelman–Rubin statistic reached 1 (213). The new CEAs were conducted in TreeAge Pro (TreeAge Software Inc., Williamstown, MA, 2009). These analyses were done in the same fashion as the original CEA ((196), chapter 2). However, the new CEAs used Bayesian ORs for non-vertebral fractures, and included an additional assumption regarding similarity of the efficacies of the K vitamins on hip, wrist and all non-vertebral fractures (Appendix: Table A4.5). Additional results and WinBUGS programs are presented in the Appendix.
4.4 Results

4.4.1 Study sample

The BRMA on vitamin K2 consisted of 10 trials including the trial by Binkley (59;63;65;71;168;170;171;216-218;220) (Figure 4.1). One of the 10 trials was done by Inoue et al (65). As the authors stratified the study population by fracture status and presented the results separately for each population, we analyzed the results of the Inoue trial separately in the URMA and in the BRMA. Also, there were another two trials done by the one research group, one trial presenting the results for BMD (217) and the second presenting the results for fractures (170). Based on our personal correspondence with Dr. Jun Iwamoto, their 2001 fracture trial (170) was assumed to be an extension of the 2000 BMD trial (217). In the BRMA, their results were assumed to belong to the same study (170;217). The BRMA on vitamin K1 consisted of five trials including the Binkley trial (60;61;63;214;219).

In total, two vitamin K2 trials (168;170) reported changes in both BMD at the lumbar spine and proportions of all or of vertebral fractures (Appendix: Table A4.1). No vitamin K2 trial reported changes in both BMD at the femoral neck and proportions of non-vertebral fractures. Four vitamin K2 trials reported complete data for clinical or X-ray confirmed vertebral fractures and non-vertebral fractures (65;168;170;171). Regarding vitamin K1, one (60) of the five included trials (60;61;63;214;219) reported both BMD-fracture endpoints at various skeletal sites (Appendix: Table A4.1).
Figure 4.1. **BRMA flow diagram (study sample).** LS and FN BMDs denote bone mineral densities at the lumbar spine and the femoral neck. VF and non-VF denote vertebral and non-vertebral fractures. N denotes a number of trials, N1 denotes a number of trials reporting the first outcome (all fractures, vertebral fractures or non-vertebral fractures), N2 denotes a number of trials reporting the second outcome (bone mineral density or non-vertebral fractures).

4.4.2 Vitamin K2: Joint effects on BMD and fractures

**Bivariate outcomes: BMD at the lumbar spine and all fractures or vertebral fractures**

The BRMAs on BMD-all fracture and BMD-vertebral fracture outcomes resulted in similar estimates of the mean treatment effects in current and future trials. Also, the posterior means of BRMAs were similar to the corresponding estimates of URMAs. For example, after adjusting for the effects on fractures, the BRMA-derived mean differences in BMD at the lumbar spine in current and future trials were 8% lower than the URMA-derived, unadjusted mean differences (*Table 4.2a*). Despite these relatively small changes in the posterior means, uncertainty around them substantially changed, as depicted by the tighter 95% CrIs. Likewise, the posterior distributions of population ORs shifted slightly: the posterior means increased by 33% or 1.33 times (from 0.6 in URMA to 0.8 in BRMA), but
the 95% CrIs around the means were more precise (Table 4.2a). Perhaps most strikingly, the widths of 95% CrIs around the posterior mean of future OR decreased fivefold compared to the widths of corresponding prediction intervals generated by the URMAs (Table 4.2a).

Probabilities of any benefit were similar when the outcomes were assessed jointly (BRMAs) or independently (URMAs). Vitamin K2 benefited both BMD at the lumbar spine and all or vertebral fractures with the probabilities \( \geq 90\% \) in current and \( \geq 67\% \) in future trials (Table 4.2a); the corresponding probabilities of benefits on either BMD or fracture outcomes were \( \geq 89\% \) and \( \geq 72\% \). However, as compared to the probabilities of clinically important benefits calculated for each outcome in the URMAs, the simultaneous detection of clinically meaningful benefits for both outcomes in the BRMAs was less likely. The probabilities of having both an increase in BMD of 1\% and a 20\% reduction of odds of all fractures (or vertebral fractures) were \( \geq 47\% \) in current and \( \geq 37\% \) in future trials. In contrast, in the URMAs, the probabilities of clinically important benefits on each outcome separately were almost two times greater (\( \geq 81\% \) and \( \geq 66\% \), current and future trials). Therefore, if we had assumed independence between the treatment effects on BMD and fracture outcomes, and just multiplied the probabilities of clinically important benefits from the URMAs, we would have mistakenly overestimated the joint benefit of vitamin K2 on both outcomes (i.e., a false positive result).

**Bivariate outcome: BMD at the femoral neck and non-vertebral fractures**

In a joint analysis of six trials (none completely reporting effects on both outcomes), the effect of vitamin K2 on BMD at the femoral neck adjusted for the effect on non-vertebral fractures remained small and uncertain, and similar to the one shown in the univariate analysis (Table 4.2a). However, the posterior distribution of the population OR for non-vertebral fractures adjusted for the effect on BMD shifted, with the posterior mean increasing from 0.5 (URMA) to 0.9 (BRMA). The widths of 95\% CrIs around the means of population and future ORs were narrower, but the intervals overlapped the OR of 1 (Table 4.2a).

Compared to the URMA-derived probabilities of any benefit on either outcome that ranged between 66\% and 90\%, the probabilities of joint benefits on both outcomes were less than 50\% (Table 4.2a). The current and future probabilities of clinically meaningful benefit on both outcomes were \( \leq 13\% \),
similar to the URMA-derived probabilities of important benefit on BMD at the femoral neck (Table 4.2a).

4.4.3 Vitamin K2: A joint effect on vertebral and non-vertebral fractures

In a bivariate analysis including the complete data, the efficacy of vitamin K2 on both vertebral and non-vertebral fractures remained inconclusive (Table 4.2b). The posterior mean of population OR for vertebral fractures increased by 14% in BRMA, from 0.7 (URMA) to 0.8 (BRMA); the mean of population OR for non-vertebral fractures increased by 40%, from 0.5 (URMA) to 0.7 (BRMA). The BRMA-derived 95% CrIs were more precise but remained wide and inconclusive (Table 4.2b), while the mean future ORs suggested fracture reductions. For instance, a future OR of vertebral fractures changed from 1.2 (95%CrI: 0.1-5.2) in the univariate analysis to 0.8 (95%CrI: 0.4-1.5) in the bivariate analysis (Table 4.2b).

The probabilities of joint benefit on vertebral and non-vertebral fractures were much smaller, compared to the estimated benefits on each outcome (Table 4.2b). The probabilities of benefits in future trials decreased up to twofold in the bivariate meta-analysis: a probability of detecting OR<1 for both vertebral and non-vertebral fractures was 80% in current and 40% in future trials (URMA: 89-94% [current], 72-78% [future]). The current and future probabilities of detecting two ORs of 0.8 were 61% and 35% (URMA: 75-87% and 62-72%).
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Analyses</th>
<th>Estimates of the pooled treatment effect</th>
<th>Probabilities of benefit on both outcomes</th>
<th>Probabilities of benefit on each outcome separately</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (95% CrI)</td>
<td>CURRENT</td>
<td>FUTURE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any benefit</td>
<td>Any benefit</td>
<td>Some benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Population MD</td>
<td>Future MD</td>
<td>Current MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Future MD</td>
<td>Future MD</td>
<td>Future MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Population OR</td>
<td>Future OR</td>
<td>Population OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Future OR</td>
<td></td>
<td>Future OR</td>
</tr>
<tr>
<td>LS BMD &amp; all fractures</td>
<td>BRMA</td>
<td>1.06 (0.1,2.1)</td>
<td>1.05 (-1.4,3.6)</td>
<td>0.74 (0.5,1.0)</td>
</tr>
<tr>
<td></td>
<td>URMA</td>
<td>1.2 (0.0,2.5)</td>
<td>1.2 (-2.3,4.8)</td>
<td>0.61 (0.2,1.4)</td>
</tr>
<tr>
<td>LS BMD &amp; VF</td>
<td>BRMA</td>
<td>1.07 (0.1,2.1)</td>
<td>1.07 (-1.4,3.6)</td>
<td>0.81 (0.5,1.1)</td>
</tr>
<tr>
<td></td>
<td>URMA</td>
<td>1.2 (0.0,2.5)</td>
<td>1.2 (-2.3,4.8)</td>
<td>0.67 (0.2,1.5)</td>
</tr>
<tr>
<td>FN BMD &amp; Non-VF</td>
<td>BRMA</td>
<td>0.13 (-0.8,1.1)</td>
<td>0.14 (-1.4,1.7)</td>
<td>0.85 (0.5,1.3)</td>
</tr>
<tr>
<td></td>
<td>URMA</td>
<td>0.1 (-0.7,0.9)</td>
<td>0.1 (-1.1,1.3)</td>
<td>0.47 (0.1,1.3)</td>
</tr>
</tbody>
</table>

BRMA denotes bivariate random-effects meta-analysis; URMA denotes univariate random-effects meta-analysis; LS and FN BMDs denote bone mineral density (BMD) at the lumbar spine and femoral neck; VF and non-VF denote vertebral fractures and non-vertebral fractures; 95% CrI denotes 95% credible interval; MD denotes the pooled mean difference in BMD; OR denotes odds ratio; Current MD and Population OR denote estimates for current trials; Future MD and Future OR denote estimates for future trials; any benefit in both outcomes is MD>0% and OR<1.0; clinically important benefit in both outcomes is MD=1% and OR=0.8; NA= not applicable.
Table 4.2b. The effect of vitamin K2 on vertebral and non-vertebral fractures: BRMA vs. URMA

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Analyses</th>
<th>Estimates of the pooled treatment effect Mean (95% CrI)</th>
<th>Probabilities of benefit on both outcomes (%)</th>
<th>Probabilities of benefit on each outcome separately (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Vertebral fractures</td>
<td>CURRENT</td>
<td>FUTURE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-vertebral fractures</td>
<td>Any benefit</td>
<td>Clinically important benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Population OR</td>
<td>Future OR</td>
<td>Population OR</td>
</tr>
<tr>
<td>VF &amp;</td>
<td>BRMA</td>
<td>0.81 (0.5,1.1)</td>
<td>0.84 (0.4,1.5)</td>
<td>0.74 (0.3,1.4)</td>
</tr>
<tr>
<td>Non-VF</td>
<td>URMA</td>
<td>0.67 (0.2,1.5)</td>
<td>1.2 (0.1,5.2)</td>
<td>0.47 (0.1,1.3)</td>
</tr>
</tbody>
</table>

BRMA denotes bivariate random-effects meta-analysis; URMA denotes univariate random-effects meta-analysis; VF and non-VF denote vertebral fractures and non-vertebral fractures; 95% CrI denotes 95% credible interval; Current and future denote the estimates for current and future studies; OR denotes odds ratio; Population and Future ORs denote pooled ORs for current and future trials; any benefit in both outcomes: ORs <1.0; clinically important benefit in both outcomes: ORs =0.8; NA= not applicable.
4.4.4 Vitamin K1: Joint effects on BMD and fractures

Similar to the conclusions of URMA, the bivariate meta-analyses showed a small and uncertain effect of vitamin K1 on BMD, after adjusting for its large effect on fractures (Table 4.3). However, we found disparities between the URMA and the BRMA estimates that seemed to depend on the skeletal site and a degree of between-study heterogeneity. The URMA and BRMA on the trabecular bone sites (e.g., BMD at the lumbar spine and vertebral fractures) yielded similar pooled MDs. These analyses combined four homogenous trials (τ=0.4). In contrast, the URMA and BRMA on the cortical bone sites (BMD at the femoral neck and non-vertebral fractures) generated quite different pooled MDs: for example, the 95% CrI around the future MD ranged from -2.5% to 4.1% in the URMA (Table 4.3); it shrank twofold in the bivariate meta-analysis (95% CrI: -0.9% to 2.2%). Also, in contrast to the analyses on the trabecular bone sites, they combined highly heterogeneous trials (τ=1.3).

We were unable to perform URMA to evaluate the effect of vitamin K1 on fractures as only one trial reported the summary estimates. However, we were able to approximate this effect in BRMA. After accounting for a small effect on BMD, the anti-fracture effect of vitamin K1 was positive but still largely uncertain in both current and future trials (Table 4.3).

Using BRMA, we also estimated the probabilities of benefits pertinent to fractures only and the probabilities of simultaneous benefits on BMD-fracture outcomes (Table 4.3). A probability of showing any reduction in odds of either vertebral or non-vertebral fractures was high: 86% in current and 95% in future trials. The corresponding probabilities of detecting OR of 0.80 were 78% and 85%. However, the BRMA-derived probabilities associated with having simultaneous increases in BMD and decreases in odds of fractures were smaller and quite different between the skeletal sites. The cortical bone sites benefited more from vitamin K1 than the trabecular bone sites. For example, at the trabecular bone sites such as BMD at the lumbar spine and vertebral fractures, the probabilities of showing any benefit on both outcomes were ≤33% in current and future trials, while the probabilities of clinically meaningful benefit were ≤10% in current and future trials. In contrast, at the cortical bone sites such as BMD at the femoral neck and non-vertebral fractures, the probabilities of any benefit were ≥75%, while the probabilities of clinical benefit were ≥46% (Table 4.3).
## Table 4.3. The effect of vitamin K1 on BMD and fractures: BRMA vs. URMA

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Analyses</th>
<th>Estimates of the pooled treatment effect</th>
<th>Probabilities of benefit on both outcomes</th>
<th>Probabilities of benefit on each outcome separately</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (95% CrI)</td>
<td>CURRENT</td>
<td>FUTURE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Population OR</td>
<td>Any benefit</td>
<td>Clinically important benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Future OR</td>
<td>&gt;0%</td>
<td>≥1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CURRENT MD</td>
<td>Future MD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;1.0</td>
<td>≤0.8</td>
</tr>
<tr>
<td>LS BMD &amp; all fractures</td>
<td>BRMA</td>
<td>-0.17 (-0.9,0.6)</td>
<td>0.89 (0.5,1.6)</td>
<td>0.91 (0.4,1.9)</td>
</tr>
<tr>
<td></td>
<td>URMA</td>
<td>-0.2 (-0.9,0.5)</td>
<td>Not estimated</td>
<td>Not estimated</td>
</tr>
<tr>
<td></td>
<td>BRMA</td>
<td>-0.18 (-0.9,0.5)</td>
<td>1.34 (0.5,1.6)</td>
<td>1.38 (0.5,3.0)</td>
</tr>
<tr>
<td></td>
<td>URMA</td>
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<td>Not estimated</td>
<td>Not estimated</td>
</tr>
<tr>
<td></td>
<td>BRMA</td>
<td>-0.18 (-0.9,0.6)</td>
<td>0.59 (0.1,1.8)</td>
<td>0.61 (0.1,1.9)</td>
</tr>
<tr>
<td></td>
<td>URMA</td>
<td>-0.2 (-0.9,0.5)</td>
<td>Not estimated</td>
<td>Not estimated</td>
</tr>
<tr>
<td></td>
<td>BRMA</td>
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<td>0.58 (-0.9,2.2)</td>
<td>0.54 (0.2,1.2)</td>
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<tr>
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<td>URMA</td>
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<td>Not estimated</td>
<td>Not estimated</td>
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<tr>
<td></td>
<td>BRMA</td>
<td>0.8 (-0.9,0.6)</td>
<td>0.91 (0.4,1.9)</td>
<td>0.91 (0.4,1.9)</td>
</tr>
<tr>
<td></td>
<td>URMA</td>
<td>-0.2 (-0.9,0.5)</td>
<td>Not estimated</td>
<td>Not estimated</td>
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<tr>
<td></td>
<td>BRMA</td>
<td>-0.18 (-0.9,0.5)</td>
<td>1.34 (0.5,1.6)</td>
<td>1.38 (0.5,3.0)</td>
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<td>URMA</td>
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<td>Not estimated</td>
<td>Not estimated</td>
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<tr>
<td></td>
<td>BRMA</td>
<td>-0.18 (-0.9,0.6)</td>
<td>0.59 (0.1,1.8)</td>
<td>0.61 (0.1,1.9)</td>
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<tr>
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<td>URMA</td>
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<td>Not estimated</td>
<td>Not estimated</td>
</tr>
<tr>
<td></td>
<td>BRMA</td>
<td>0.58 (-0.2,1.5)</td>
<td>0.58 (-0.9,2.2)</td>
<td>0.54 (0.2,1.2)</td>
</tr>
<tr>
<td></td>
<td>URMA</td>
<td>0.7 (-0.7,2.4)</td>
<td>Not estimated</td>
<td>Not estimated</td>
</tr>
</tbody>
</table>

**Notes:**
- BRMA denotes bivariate random-effects meta-analysis; URMA denotes univariate random-effects meta-analysis; § reference analysis; 95% CrI denotes 95% credible interval; LS and FN BMDs denote bone mineral density (BMD) at the lumbar spine and femoral neck; VF and non-VF denote vertebral fractures and non-vertebral fractures; MD denotes the pooled mean difference in BMD; OR denotes odds ratio; any benefit in both outcomes is MD>0% and OR<1.0; clinically important benefit in both outcomes is MD=1% and OR=0.8; * estimated in BRMA; NA= not applicable.
4.4.5 Estimation of the between-study correlation and the between-study variance

In the BRMA of vitamin K2 effect on BMD at the femoral neck and non-vertebral fractures and the BRMAs of vitamin K1 effect on BMD and fractures at various skeletal sites, we found a small negative between-study correlation with the values of $\rho_b$ ranging between -0.01 to -0.03 (95%CrIs: -0.8 to 0.8) (Table 4.4 and Figure 4.2). These analyses were similar in terms of three factors: between-study heterogeneity (small: $\tau < 0.6$ (138)), number of pooled trials (i.e., small) and amount of missing outcomes (i.e., large: 0 of 6 combined (K2) and 1 of 4 combined (K1) reported both outcomes).

In contrast, in the BRMAs that had a larger number of highly heterogeneous vitamin K2 trials ($\tau > 0.9$) with two of 10 trials that completely reported both endpoints, estimation of the between-study correlation was poor but the point estimate was not zero (mean $\rho_b = -0.2$ (95%CrI: -0.9 to 0.9) (Table 4.4 and Figure 4.2). A moderate negative value of $\rho_b$ (mean:- 0.2/median:-0.4) suggested an expected opposite direction of changes in BMD at the lumbar spine and odds of fractures across all vitamin K2 trials.

In the BRMA of completely reported binary outcomes, the between-study correlation suggested an expected direction of the treatment effect (Table 4.4 and Figure 4.2c). Its value was small and positive ($\rho_b = 0.2$, 95%CrI: -0.7 to 0.9), suggesting that odds of vertebral and non-vertebral fractures likely changed in the same direction across all combined vitamin K2 trials.

As compared to the estimates of between-study standard deviation (\(\tau\)-s) in URMAs, in most BRMAs that included incomplete data, the point estimates of the between-study standard deviation on both outcomes were at least twofold smaller; their 95% CrIs were more precisely defined (Table 4.5). For example, in the vitamin K2 BRMA on BMD at the femoral neck and non-vertebral fractures, the 95% CrI around $\tau$ of the BMD outcome shrank fivefold (URMA 95%CrI: 0.3-1.7 vs. BRMA 95%CrI: 0.1-0.4). Similar shrinkages of the variance distributions were found in the BRMA including five trials that completely reported the treatment effects on vertebral and non-vertebral fractures.
<table>
<thead>
<tr>
<th>BRMA</th>
<th>Outcomes</th>
<th>Priors on between-study correlation ρ_b</th>
<th>Between-study correlation ρ_b Mean/Median (95% CrI)</th>
<th>Pooled treatment effect Mean (95% CrI)</th>
<th>Probabilities of benefit on both outcomes %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Current MD</td>
<td>Future MD</td>
<td>Population OR</td>
</tr>
<tr>
<td>Vitamin K2</td>
<td>LS BMD &amp; all fractures</td>
<td>Bisphosphonates (reference)</td>
<td>-0.2/ -0.4 (-0.9,0.9)</td>
<td>1.1 (0.1,2.1)</td>
<td>1.1 (-1.4,3.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin D3 and calcium</td>
<td>-0.2 / -0.8 (-1.0,1.0)</td>
<td>1.3 (0.1,2.6)</td>
<td>1.3 (-2.1,4.8)</td>
</tr>
<tr>
<td></td>
<td>FN BMD &amp; Non-VF</td>
<td>Bisphosphonates (reference)</td>
<td>-0.02 / -0.03 (-0.8,0.8)</td>
<td>0.1 (-0.8,1.1)</td>
<td>0.1 (-1.4,1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin D3 and calcium</td>
<td>-0.1 / -0.3 (-1.0,1.0)</td>
<td>0.3 (-1.0,2.3)</td>
<td>0.3 (-2.4,3.5)</td>
</tr>
<tr>
<td>Vitamin K1</td>
<td>LS BMD &amp; all fractures</td>
<td>Bisphosphonates (reference)</td>
<td>-0.01 / -0.01 (-0.8,0.8)</td>
<td>-0.2 (-0.9,0.6)</td>
<td>-0.2 (-1.5,1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin D3 and calcium</td>
<td>0.04 / 0.09 (-1.0,1.0)</td>
<td>-0.2 (-1.0,8)</td>
<td>-0.2 (-2.1,1.8)</td>
</tr>
<tr>
<td></td>
<td>FN BMD &amp; Non-VF</td>
<td>Bisphosphonates (reference)</td>
<td>-0.02 / -0.03 (-0.8,0.8)</td>
<td>0.6 (-0.2,1.5)</td>
<td>0.6 (-0.9,2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin D3 and calcium</td>
<td>0.04 / 0.1 (-1.0,1.0)</td>
<td>0.7 (-0.5,2.1)</td>
<td>0.7 (-1.9,3.5)</td>
</tr>
</tbody>
</table>

95% CrI denotes 95% credible interval; MD denotes the pooled mean difference in bone mineral density (BMD); OR denotes odds ratio; any benefit on both outcomes is MD>0% and OR<1.0; clinically important benefit on both outcomes is MD=1% and OR=0.8; LS and FN BMDs denote bone mineral density (BMD) at the lumbar spine and femoral neck; non-VF denotes non-vertebral fractures; † medians.
Figure 4.2. Posterior distributions for the between-study correlation: vitamin K2 and vitamin K1. The between-study correlation is denoted as $\rho_b$. Panel A: BRMA on vitamin K2 at the lumbar spine BMD (bone mineral density) and all fractures. Panel B: BRMA on vitamin K2 at the femoral neck BMD and non-vertebral fractures. Panel C: BRMA on vitamin K2 for vertebral and non-vertebral fractures. Panel D: BRMA on vitamin K1 at lumbar spine BMD and all fractures (similar posteriors obtained for other vitamin K1 BRMAs).
Table 4.5. Estimation of the between-study standard deviation: BRMA vs. URMA

<table>
<thead>
<tr>
<th>OUTCOMES</th>
<th>VITAMIN K2</th>
<th>VITAMIN K1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Between-study standard deviation τ</td>
<td>Mean (95% CrI)</td>
</tr>
<tr>
<td></td>
<td>BRMA</td>
<td>URMA</td>
</tr>
<tr>
<td>LS BMD [1] &amp; all fractures [2]</td>
<td>(\tau[1]=0.3) (0.1,0.5) (\tau[2]=1.2) (0.6,1.9)</td>
<td>(\tau[1]=0.9) (0.3,1.7) (\tau[2]=1.6) (0.9,2.2)</td>
</tr>
<tr>
<td>FN BMD [1] &amp; Non-VF [2]</td>
<td>(\tau[1]=0.6) (0.2,1.2) (\tau[2]=0.2) (0.1,0.4)</td>
<td>(\tau[1]=0.3) (0.0,1.5) (\tau[2]=1.2) (0.3,1.7)</td>
</tr>
<tr>
<td>VF [1] &amp; nonVF [2]</td>
<td>(\tau[1]=0.3) (0.1,0.6) (\tau[2]=0.6) (0.2,1.1)</td>
<td>(\tau[1]=1.2) (0.3,1.7) (\tau[2]=0.3) (0.0,1.5)</td>
</tr>
</tbody>
</table>

BRMA denotes bivariate random-effects meta-analysis; URMA denotes univariate random-effects meta-analysis; 95% CrI denotes 95% credible interval; LS and FN BMDs denote bone mineral density (BMD) at the lumbar spine and femoral neck; VF and non-VF denote vertebral fractures and non-vertebral fractures; [1] and [2] denote the first and second outcome; § only one vitamin K1 trial reported fractures; NA = not applicable.
4.4.6 Sensitivity analyses

We examined robustness of the outputs of BRMAs to changes in assumptions on the within- and between-study correlations. Outputs of all BRMAs remained robust to the changes of the values of the within-study correlation coefficient (Appendix: Tables A4.4).

In contrast, using a different set of data to estimate the between-study correlation greatly affected the outputs of BRMAs. The reference analysis “borrowed strength” from 14 relatively homogeneous bisphosphonate trials to enhance estimation of the between-study correlation (Table 4.4 and Appendix: Tables A4.2 and A4.3). Sensitivity analyses used the data of three heterogeneous vitamin D trials (τ >1.4, Appendix: Table A4.3) and found substantial changes in all outputs (Table 4.4). For example, the point estimates and their 95% CrIs, particularly those of predictions, became similar to the posteriors generated by the URMAs. In addition, estimation of the between-study correlations became worse (95% CrIs: -1 to +1), depicted with the bimodal posteriors.

An additional sensitivity analysis on the prior specified for the variance-covariance matrix showed that the posterior means for \( \rho_b \) were different for different values of the mean of the Wishart priors, but estimation of \( \rho_b \) as defined by the 95% CrIs remained poor (Table 4.6). Also, important changes in the estimates of between-study variance, covariance and \( \rho_b \) were found. For example, in all BRMAs, differences in the estimates of \( \rho_b \) became large when the mean of inverse Wishart reflected small between-study heterogeneity (τ-s: 0.1-0.2 (138)). In addition, the point estimates of the pooled treatment effects in current and future studies were robust to the choice of the mean parameter of an inverse Wishart prior; however, their 95% CrIs changed (Figure 4.3 and Table 4.6). The Wishart prior with large between-study variances on both outcomes resulted in wide 95% CrIs around the pooled means, while the Wishart prior with small between-study variances on both outcomes resulted in narrow 95% CrIs around the pooled means. These fluctuations were more pronounced for the 95% CrIs around the true mean effects in future trials. Nonetheless, in all analyses, credible intervals overlapped the zero effect, confirming the uncertainties in the efficacies of the K vitamins on both BMD and fractures.
Table 4.6. Sensitivity of the outputs of Bayesian BRMA to an inverse Wishart prior on the variance-covariance matrix

<table>
<thead>
<tr>
<th>BRMA</th>
<th>Wishart Priors</th>
<th>Current MD</th>
<th>Future MD</th>
<th>Current OR</th>
<th>Future OR</th>
<th>Between-study correlation</th>
<th>Variance &amp; covariance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean/Median (95% Credible Interval )</td>
<td></td>
<td></td>
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<tr>
<td>Vitamin K2: LS BMD and all fractures</td>
<td>Reference $\tau^2$: $\Omega^{-1} \sim Wish\left(\begin{bmatrix} 0.09 &amp; 0 \ 0 &amp; 0.5 \end{bmatrix},3\right)$, $\tau[1]=0.3$, $\tau[2]=0.7$</td>
<td>1.1/1.1 (0.1,1.21)</td>
<td>1.1/1.0 (-1.4,3.6)</td>
<td>0.8/0.8 (0.4,1.0)</td>
<td>0.8/0.8 (0.4,1.4)</td>
<td>-0.2/-0.4 (-0.9,0.9)</td>
<td>$D[1,1]=0.1/0.1 (0.0,0.2)$, $D[2,2]=1.4/1.1 (0.3,3.7)$</td>
</tr>
<tr>
<td>N1=4 N2=8</td>
<td>Very large $\tau^2$: $\Omega^{-1} \sim Wish\left(\begin{bmatrix} 1 &amp; 0 \ 0 &amp; 1 \end{bmatrix},3\right)$, $\tau[1]=1$, $\tau[2]=1$</td>
<td>1.1/1.1 (0.2,2.1)</td>
<td>1.1/1.1 (-1.4,3.7)</td>
<td>0.7/0.7 (0.4,1.1)</td>
<td>0.8/0.7 (0.2,1.8)</td>
<td>-0.1/-0.2 (-0.8,0.6)</td>
<td>$D[1,1]=0.2/0.2 (0.1,0.4)$, $D[2,2]=1.4/1.2 (0.4,3.7)$</td>
</tr>
<tr>
<td></td>
<td>Large $\tau^2$: $\Omega^{-1} \sim Wish\left(\begin{bmatrix} 0.5 &amp; 0 \ 0 &amp; 0.5 \end{bmatrix},3\right)$, $\tau[1]=0.7$, $\tau[2]=0.7$</td>
<td>1.1/1.1 (0.2,2.1)</td>
<td>1.1/1.1 (-1.3,3.6)</td>
<td>0.7/0.7 (0.5,1.1)</td>
<td>0.8/0.7 (0.3,1.6)</td>
<td>-0.2/-0.3 (-0.8,0.7)</td>
<td>$D[1,1]=0.1/0.1 (0.0,0.3)$, $D[2,2]=1.3/1.0 (0.3,3.5)$</td>
</tr>
<tr>
<td></td>
<td>Small $\tau^2$: $\Omega^{-1} \sim Wish\left(\begin{bmatrix} 0.01 &amp; 0 \ 0 &amp; 0.03 \end{bmatrix},3\right)$, $\tau[1]=0.1$, $\tau[2]=0.2$</td>
<td>1.0/1.0 (0.1,2.0)</td>
<td>1.0/1.0 (-1.4,3.5)</td>
<td>0.8/0.8 (0.5,1.0)</td>
<td>0.8/0.8 (0.4,1.4)</td>
<td>-0.8/-1.0 (-1.0,1.0)</td>
<td>$D[1,1]=0.1/0.1 (0.0,0.2)$, $D[2,2]=1.3/1.1 (0.3,3.6)$</td>
</tr>
<tr>
<td>Vitamin K2: FN BMD and non-vertebral fractures</td>
<td>Reference $\tau^2$: $\Omega^{-1} \sim Wish\left(\begin{bmatrix} 0.09 &amp; 0 \ 0 &amp; 0.5 \end{bmatrix},3\right)$, $\tau[1]=0.3$, $\tau[2]=0.7$</td>
<td>0.1/0.1 (-0.8,1.1)</td>
<td>0.1/0.1 (-1.4,1.7)</td>
<td>0.9/0.8 (0.5,1.3)</td>
<td>0.9/0.8 (0.4,1.6)</td>
<td>-0.02/-0.03 (-0.8,0.8)</td>
<td>$D[1,1]=0.0/0.0 (0.0,0.1)$, $D[2,2]=0.3/0.2 (0.1,1.4)$</td>
</tr>
<tr>
<td>N1=4 N2=2</td>
<td>Very large $\tau^2$: $\Omega^{-1} \sim Wish\left(\begin{bmatrix} 1 &amp; 0 \ 0 &amp; 1 \end{bmatrix},3\right)$, $\tau[1]=1$, $\tau[2]=1$</td>
<td>0.1/0.1 (-1.0,1.3)</td>
<td>0.1/0.1 (-1.7,2.0)</td>
<td>0.8/0.8 (0.4,1.4)</td>
<td>0.9/0.8 (0.3,2.0)</td>
<td>-0.01/-0.01 (-0.6,0.6)</td>
<td>$D[1,1]=0.2/0.1 (0.1,0.4)$, $D[2,2]=0.5/0.3 (0.1,2.0)$</td>
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<tr>
<td></td>
<td>Large $\tau^2$: $\Omega^{-1} \sim Wish\left(\begin{bmatrix} 0.5 &amp; 0 \ 0 &amp; 0.5 \end{bmatrix},3\right)$, $\tau[1]=0.7$, $\tau[2]=0.7$</td>
<td>0.1/0.1 (-0.8,1.1)</td>
<td>0.1/0.1 (-1.3,1.5)</td>
<td>0.8/0.8 (0.5,1.3)</td>
<td>0.9/0.8 (0.3,1.8)</td>
<td>-0.01/-0.01 (-0.7,0.6)</td>
<td>$D[1,1]=0.1/0.1 (0.0,0.2)$, $D[2,2]=0.3/0.2 (0.1,1.2)$</td>
</tr>
<tr>
<td></td>
<td>Small $\tau^2$: $\Omega^{-1} \sim Wish\left(\begin{bmatrix} 0.01 &amp; 0 \ 0 &amp; 0.03 \end{bmatrix},3\right)$, $\tau[1]=0.1$, $\tau[2]=0.2$</td>
<td>0.1/0.1 (-0.5,0.7)</td>
<td>0.1/0.1 (-0.6,0.9)</td>
<td>0.9/0.8 (0.6,1.3)</td>
<td>0.9/0.8 (0.5,1.4)</td>
<td>-0.03/-0.07 (-1.0,1.0)</td>
<td>$D[1,1]=0.0/0.0 (0.0,0.1)$, $D[2,2]=0.1/0.0 (0.0,0.3)$</td>
</tr>
<tr>
<td>BRMA</td>
<td>Wishart Priors</td>
<td>Current MD/OR$^\S$</td>
<td>Future MD/OR$^\S$</td>
<td>Current OR</td>
<td>Future OR</td>
<td>Between-study correlation</td>
<td>Variance &amp; covariance</td>
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<td><strong>Vitamin K2$^\S$:</strong></td>
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<tr>
<td>vertebral fractures</td>
<td>Reference $\tau^2$:</td>
<td>0.8/0.8 (0.5,1.1)</td>
<td>0.8/0.8 (0.4,1.5)</td>
<td>0.7/0.7</td>
<td>0.9/0.7</td>
<td>0.2/0.3 (-0.7,0.9)</td>
<td>D[1,1]= 0.1/0.3 (0.0,0.4)</td>
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<td>and non-vertebral fractures</td>
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<td></td>
<td>D[1,2]= 0.1/0.0 (-0.1,0.5)</td>
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<tr>
<td>N1=4</td>
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<td>D[2,2]= 0.3/0.2 (0.1,1.3)</td>
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<td>N2=4</td>
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<td><strong>Vitamin K1:</strong></td>
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<tr>
<td>LS BMD and all fractures</td>
<td>Reference $\tau^2$:</td>
<td>-0.2/-0.2 (-0.9,0.6)</td>
<td>-0.2/-0.2 (-1.5,1.2)</td>
<td>0.9/0.8</td>
<td>0.9/0.8</td>
<td>-0.01/-0.01 (-0.8,0.8)</td>
<td>D[1,1]= 0.1/0.0 (0.0,0.1)</td>
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<td></td>
<td>D[1,2]= -0.0/-0.0 (-0.2,0.1)</td>
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<tr>
<td>N2=4</td>
<td></td>
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<td></td>
<td>D[2,2]= 0.3/0.2 (0.1,1.1)</td>
</tr>
<tr>
<td></td>
<td>Very large $\tau^2$:</td>
<td>-0.2/-0.2 (-1.0,0.6)</td>
<td>-0.2/-0.2 (-1.7,1.4)</td>
<td>0.9/0.8</td>
<td>1.0/0.9</td>
<td>-0.01/-0.01 (-0.6,0.6)</td>
<td>D[1,1]= 0.2/0.2 (0.1,0.4)</td>
</tr>
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<td></td>
<td></td>
<td>D[1,2]= -0.0/-0.0 (-0.2,0.2)</td>
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<td></td>
<td>D[2,2]= 0.4/0.3 (0.1,1.4)</td>
</tr>
<tr>
<td></td>
<td>Small $\tau^2$:</td>
<td>-0.2/-0.2 (-0.9,0.5)</td>
<td>-0.2/-0.2 (-1.4,1.1)</td>
<td>0.9/0.8</td>
<td>1.0/0.8</td>
<td>-0.01/-0.01 (-0.7,0.7)</td>
<td>D[1,1]= 0.1/0.1 (0.0,0.3)</td>
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<td></td>
<td>D[1,2]= -0.0/-0.0 (-0.2,0.2)</td>
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<td></td>
<td>D[2,2]= 0.2/0.2 (0.1,0.9)</td>
</tr>
</tbody>
</table>

$^\S$ Mean/Median (95% Credible Interval)
<table>
<thead>
<tr>
<th>BRMA</th>
<th>Wishart Priors</th>
<th>Current MD</th>
<th>Future MD</th>
<th>Current OR</th>
<th>Future OR</th>
<th>Between-study correlation</th>
<th>Variance &amp; covariance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K1: FN BMD and non-vertebral fractures</td>
<td>Reference $\tau^2$: $\Omega^{-1} \sim Wish \left( \begin{pmatrix} 0.09 &amp; 0 \ 0 &amp; 0.5 \end{pmatrix}, 3 \right)$, $\tau[1]=0.3$, $\tau[2]=0.7$</td>
<td>0.6/0.6 (-0.2,1.5)</td>
<td>0.6/0.6 (-0.9,2.2)</td>
<td>0.5/0.5 (0.2,1.2)</td>
<td>0.6/0.5 (0.2,1.3)</td>
<td>-0.02/-0.03 (-0.8,0.8)</td>
<td>$D[1,1]=0.1/0.0 (0.0,0.1)$, $D[1,2]=-0.0/0.0 (-0.2,0.2)$, $D[2,2]=0.4/0.3 (0.1,1.6)$</td>
</tr>
<tr>
<td>N1=1 N2=4</td>
<td>Very large $\tau^2$: $\Omega^{-1} \sim Wish \left( \begin{pmatrix} 1 &amp; 0 \ 0 &amp; 1 \end{pmatrix}, 3 \right)$, $\tau[1]=1$, $\tau[2]=1$</td>
<td>0.6/0.6 (-0.3,1.7)</td>
<td>0.6/0.6 (-1.1,2.5)</td>
<td>0.6/0.5 (0.2,1.4)</td>
<td>0.6/0.5 (0.1,1.9)</td>
<td>-0.002/-0.002 (-0.6,0.6)</td>
<td>$D[1,1]=0.2/0.2 (0.1,0.4)$, $D[1,2]=-0.0/0.0 (-0.3,0.3)$, $D[2,2]=0.6/0.4 (0.1,2.0)$</td>
</tr>
<tr>
<td></td>
<td>Large $\tau^2$: $\Omega^{-1} \sim Wish \left( \begin{pmatrix} 0.5 &amp; 0 \ 0 &amp; 0.5 \end{pmatrix}, 3 \right)$, $\tau[1]=0.7$, $\tau[2]=0.7$</td>
<td>0.6/0.5 (-0.2,1.5)</td>
<td>0.6/0.5 (-0.8,2.1)</td>
<td>0.6/0.5 (0.2,1.3)</td>
<td>0.6/0.5 (0.1,1.6)</td>
<td>-0.01/-0.01 (-0.7,0.7)</td>
<td>$D[1,1]=0.1/0.1 (0.0,0.3)$, $D[1,2]=-0.0/0.0 (-0.2,0.2)$, $D[2,2]=0.6/0.2 (0.1,1.4)$</td>
</tr>
<tr>
<td></td>
<td>Small $\tau^2$: $\Omega^{-1} \sim Wish \left( \begin{pmatrix} 0.01 &amp; 0 \ 0 &amp; 0.03 \end{pmatrix}, 3 \right)$, $\tau[1]=0.1$, $\tau[2]=0.2$</td>
<td>0.5/0.5 (-0.1,1.1)</td>
<td>0.5/0.4 (-0.4,1.4)</td>
<td>0.5/0.5 (0.2,1.0)</td>
<td>0.5/0.5 (0.2,1.1)</td>
<td>+0.01/0.01 (-1.0,1.0)</td>
<td>$D[1,1]=0.1/0.0 (0.0,0.1)$, $D[1,2]=-0.0/0.0 (-0.2,0.2)$, $D[2,2]=0.4/0.3 (0.1,1.6)$</td>
</tr>
</tbody>
</table>

BRMA denotes bivariate random-effects meta-analysis; MD denotes a posterior estimate for the pooled mean difference in current or future trials; OR denotes a posterior estimate for the odds ratio in current or future trials; LS BMD and FN BMD denote bone mineral density at the lumbar spine and femoral neck, respectively; $\tau$ denotes between-study standard deviation; $[1]$ and $[2]$ denote the first and the second components of bivariate outcomes: in the BMD-fracture outcomes $[1]$ represents the fracture outcome and $[2]$ represents BMD while in the binary bivariate fracture outcome, $[1]$ represents vertebral fractures and $[2]$ represents non-vertebral fractures; N1 denotes a number of studies completely reporting outcome 1 (e.g., fractures) and N2 denotes a number of studies completely reporting outcome 2 (e.g., BMD); Wish denotes a Wishart distribution; $\Omega$ denotes the precision matrix; $D[1,1]$ and $D[2,2]$ denote estimates of the between-study variance for the first and the second component of the bivariate outcomes; $D[1,2]$ denotes estimates of the covariance; maps the only BRMA that included two binary (fracture) outcomes.
Figure 4.3. Sensitivity of posterior means (current and future studies) to different values of the mean of the Wishart prior. MD denotes mean difference in BMD; OR denotes odds ratio; 1, 2, 3 and 4 denote four different Wishart priors where case 1 represents reference analysis, case 2 represents a Wishart prior with very large between-study standard deviations on both outcomes ($\tau_1=1$, $\tau_2=1$), case 3 represents a Wishart prior with very relatively large between-study standard deviations on both outcomes ($\tau_1=0.5$, $\tau_2=0.5$) and case 4 represents a Wishart prior with small between-study standard deviations on both outcomes ($\tau_1=0.01$, $\tau_2=0.03$). N1 denotes a number of studies completely reporting outcome 1 (e.g., fractures) and N2 denotes a number of studies completely reporting outcome 2 (e.g., BMD); 95%Crl denotes 95% credible interval.
4.4.7 Application to cost-effectiveness analysis

We examined changes in incremental cost-effectiveness of the vitamin K2 and vitamin K1 strategies after populating the model with the treatment efficacy estimates derived in the URMA and the BRMA (Appendix: Table A4.5). The Bayesian population and future ORs caused changes of the distributions around the incremental effects (QALYs) and the incremental costs (Tables 4.7 and 4.8). The incremental effectiveness of the vitamin K2 strategy reversed from statistically significant in the original analysis (incremental QALYs: 0.7, 95% CrI: 0.2, 1.3) to statistically non-significant in the analyses using the treatment effects of the URMA (0.5, 95% CrI: -0.4, 1.2) and the BRMA (0.1, 95%CrI:-0.7, 0.7) (Table 4.7). In the new CEAs, the incremental costs of the vitamin K2 strategy also changed and significantly increased (i.e., no negative costs or savings). The Bayesian bivariate ORs did not change the incremental cost-effectiveness of the vitamin K1 strategy, as compared to the original results (Table 4.8). For example, the distributions around the incremental effectiveness of the vitamin K1 strategy shrank but the mean incremental QALYs remained the same (future OR: 0.4 [95%CrI: -0.7, 1.2] vs. original OR: 0.4 [95%CrI: -1.9, 1.4]); the mean incremental costs became negative, indicating savings.

The changes in the incremental estimates caused important changes in the ICER. In the CEA using the population ORs of the Bayesian univariate meta-analysis, the vitamin K2 strategy cost less than $50,000/QALY (ICER: $21,521/QALY gained) (Table 4.7). However, using the future ORs of the Bayesian bivariate meta-analysis, the vitamin K2 strategy cost more than $100,000/QALY (ICER: $118,636/QALY gained). Using the future ORs of the bivariate meta-analysis, the vitamin K1 strategy was cost-saving (Table 4.7).

In the new analyses, the probabilities of cost-effectiveness of the vitamin K2 and vitamin K1 strategies also changed. At a willingness-to-pay threshold of $50,000/QALY, the probability of cost-effectiveness of the vitamin K2 strategy steeply decreased by approximately 60%, from 95% in the original CEA to 35% in the CEA using BRMA-derived ORs (Appendix: Figure A4.1). At the same threshold, the probability of cost-effectiveness of the vitamin K1 strategy increased from 80% in the original analysis to 90% in the new analyses (Appendix: Figure A4.2). In all CEAs, values of the population EVPI fluctuated but remained large, indicating considerable decision uncertainty (Tables 4.7 and 4.8).
Table 4.7. Discounted lifetime costs and benefits (QALYs): Vitamin K2 – published, URMA-derived and BRMA-derived ORs for the efficacy of vitamin K2

<table>
<thead>
<tr>
<th>Analysis Strategies</th>
<th>Outcomes §, †, ‡</th>
<th>Incremental Changes</th>
<th>Population EVPI † at $50,000/QALY, $ in billions</th>
<th>Costs, $US †</th>
<th>QALYs ‡</th>
<th>Costs, $US †</th>
<th>QALYs ‡</th>
<th>Incremental Cost-Effectiveness Ratio: Cost ($) / QALY gained</th>
<th>EVPI per person, $</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin K2 (original)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Incremental (Cost ($)) / QALY gained</td>
<td></td>
</tr>
<tr>
<td>No supplementation</td>
<td>19,190</td>
<td>18.70</td>
<td></td>
<td>(12,335; 28,469)</td>
<td>(18.22; 19.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D3 with calcium</td>
<td>14,994</td>
<td>19.13</td>
<td></td>
<td>(9,364; 23,605)</td>
<td>(18.28; 19.81)</td>
<td>- 4,196</td>
<td>(- 9,015; 520)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Vitamin K2, vitamin D3 &amp; calcium</td>
<td>23,950</td>
<td>19.86</td>
<td></td>
<td>(14,306; 38,653)</td>
<td>(19.16; 20.45)</td>
<td>- 2,616; 23,752</td>
<td>(0.19; 1.31)</td>
<td>12,268</td>
<td>28.9 (1,112)</td>
</tr>
<tr>
<td><strong>Vitamin K2 (Bayesian URMA) †</strong></td>
<td></td>
<td></td>
<td></td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Incremental (Cost ($)) / QALY gained</td>
<td></td>
</tr>
<tr>
<td>No supplementation</td>
<td>19,190</td>
<td>18.70</td>
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<td>(12,335; 28,469)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D3 with calcium</td>
<td>14,994</td>
<td>19.13</td>
<td></td>
<td>(9,364; 23,605)</td>
<td>(18.28; 19.81)</td>
<td>- 4,196</td>
<td>(- 9,015; 520)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Vitamin K2, vitamin D3 &amp; calcium</td>
<td>26,400</td>
<td>19.66</td>
<td></td>
<td>(15,912; 43,236)</td>
<td>(18.36; 20.34)</td>
<td>11,406</td>
<td>(220,27,630)</td>
<td>(0.19; 1.31)</td>
<td>21,521</td>
</tr>
<tr>
<td><strong>Vitamin K2 (BRMA) †</strong></td>
<td></td>
<td></td>
<td></td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Incremental (Cost ($)) / QALY gained</td>
<td></td>
</tr>
<tr>
<td>No supplementation</td>
<td>19,190</td>
<td>18.70</td>
<td></td>
<td>(12,335; 28,469)</td>
<td>(18.22; 19.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D3 with calcium</td>
<td>14,994</td>
<td>19.13</td>
<td></td>
<td>(9,364; 23,605)</td>
<td>(18.28; 19.81)</td>
<td>- 4,196</td>
<td>(- 9,015; 520)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Vitamin K2, vitamin D3 &amp; calcium</td>
<td>30,692</td>
<td>19.34</td>
<td></td>
<td>(20,190; 43,714)</td>
<td>(18.48; 20.02)</td>
<td>15,698</td>
<td>(6,819; 27,499)</td>
<td>(0.29; 0.61)</td>
<td>74,752</td>
</tr>
<tr>
<td><strong>Vitamin K2 (BRMA) ¹</strong></td>
<td></td>
<td></td>
<td></td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Mean (95% CrI)</td>
<td>Incremental (Cost ($)) / QALY gained</td>
<td></td>
</tr>
<tr>
<td>No supplementation</td>
<td>19,190</td>
<td>18.70</td>
<td></td>
<td>(12,335; 28,469)</td>
<td>(18.22; 19.17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D3 with calcium</td>
<td>14,994</td>
<td>19.13</td>
<td></td>
<td>(9,364; 23,605)</td>
<td>(18.28; 19.81)</td>
<td>- 4,196</td>
<td>(- 9,015; 520)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>Vitamin K2, vitamin D3 &amp; calcium</td>
<td>31,603</td>
<td>19.27</td>
<td></td>
<td>(19,709; 48,876)</td>
<td>(18.11; 20.02)</td>
<td>16,609</td>
<td>(5,933; 31,377)</td>
<td>(-0.71; 0.74)</td>
<td>118,636</td>
</tr>
</tbody>
</table>

§ Costs and benefits discounted at 3% per year; † Costs in 2009 USD; ‡ QALY denotes quality-adjusted life year; CrI denotes credible interval; EVPI denotes the expected value of perfect information; † population = 26 million; † Population odds ratio (OR); ¹ Future OR.
Table 4.8. Discounted lifetime costs and benefits (QALYs): Vitamin K1 – published, URMA-derived and BRMA-derived ORs for the efficacy of vitamin K1

<table>
<thead>
<tr>
<th>Analysis Strategies</th>
<th>Outcomes $, †, ‡</th>
<th>Incremental Changes</th>
<th>Incremental Cost-Effectiveness Ratio (ICER): Cost ($)/QALY gained</th>
<th>Population EVPI, at $50,000/QALY, $ in billions (EVPI per person, $)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Costs, $US † Mean (95% CrI)</td>
<td>QALYs ‡ Mean (95% CrI)</td>
<td>Costs, $US † Mean (95% CrI)</td>
<td>QALYs ‡ Mean (95% CrI)</td>
</tr>
<tr>
<td><strong>Vitamin K1 (original)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No supplementation</td>
<td>19,028 (11,976; 28,066)</td>
<td>18.71 (18.24; 19.15)</td>
<td>- 4,283 (-9,307; 288)</td>
<td>0.45 (-0.22; 0.89)</td>
</tr>
<tr>
<td>Vitamin D3 with calcium</td>
<td>14,745 (9,269; 22,577)</td>
<td>19.16 (18.38; 19.78)</td>
<td>(-9,307; 288) (-0.22; 0.89)</td>
<td>0.42</td>
</tr>
<tr>
<td>Vitamin K1, vitamin D3 &amp; calcium</td>
<td>18,759 (5,138; 91,188)</td>
<td>19.58 (17.41; 20.44)</td>
<td>(-13,740; 78,154) (-1.89; 1.41)</td>
<td>9,557</td>
</tr>
<tr>
<td><strong>Vitamin K1 (Bayesian BRMA) 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No supplementation</td>
<td>19,028 (11,976; 28,066)</td>
<td>18.71 (18.24; 19.15)</td>
<td>- 4,283 (-9,307; 288)</td>
<td>0.45 (-0.22; 0.89)</td>
</tr>
<tr>
<td>Vitamin D3 with calcium</td>
<td>14,745 (9,269; 22,577)</td>
<td>19.16 (18.38; 19.78)</td>
<td>(-9,307; 288) (-0.22; 0.89)</td>
<td>0.47</td>
</tr>
<tr>
<td>Vitamin K1, vitamin D3 &amp; calcium</td>
<td>12,962 (7,318; 24,151)</td>
<td>19.63 (18.38; 20.30)</td>
<td>(-9,346; 7,189) (-0.46; 1.22)</td>
<td>cost saving</td>
</tr>
<tr>
<td><strong>Vitamin K1 (Bayesian BRMA) 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No supplementation</td>
<td>19,028 (11,976; 28,066)</td>
<td>18.71 (18.24; 19.15)</td>
<td>- 4,283 (-9,307; 288)</td>
<td>0.45 (-0.22; 0.89)</td>
</tr>
<tr>
<td>Vitamin D3 with calcium</td>
<td>14,745 (9,269; 22,577)</td>
<td>19.16 (18.38; 19.78)</td>
<td>(-9,307; 288) (-0.22; 0.89)</td>
<td>0.40</td>
</tr>
<tr>
<td>Vitamin K1, vitamin D3 &amp; calcium</td>
<td>13,592 (7,539; 26,278)</td>
<td>19.56 (18.14; 20.33)</td>
<td>(-8,924; 9,823) (-0.72; 1.17)</td>
<td>cost saving</td>
</tr>
</tbody>
</table>

$ Costs and benefits discounted at 3% per year; † Costs in 2009 USD; ‡ QALY denotes quality-adjusted life year; CrI denotes credible interval; EVPI denotes the expected value of perfect information; 1 population = 26 million; 1 Population odds ratio (OR); 2 Future OR
4.5 Discussion

We examined the effects of vitamin K2 and vitamin K1 on BMD and fractures when these two outcomes were modeled jointly. These bivariate meta-analyses included small numbers of trials, many with incompletely reported treatment effects on either of two bone outcomes. In most analyses, BRMA resulted in more precise estimates of the pooled treatment effect in current and future trials. In all bivariate meta-analyses, the pooled treatment estimates remained inconclusive or insignificant (in the sense that the posterior 95% CrIs did not exclude null values). Vitamin K2 benefited both BMD at the lumbar spine and vertebral fractures with the odds 9 to 1 and 2 to 1 in current and in future studies; but the odds of clinically important benefits on both outcomes were less than 1 (odds of 0.9 and 0.6 in current and future studies, Table 4.2a). Also, based on the available data and as compared to control treatment, the anticipated odds of any important benefit of vitamin K2 on both BMD at the femoral neck and non-vertebral fractures were equal (1 – 1); the odds of improving BMD at the femoral neck by 1% and reducing fractures by 20% were nil (Table 4.2a). However, given the limited quality of vitamin K trials, particularly those assessing fractures, inconclusive treatment estimates and discrepant posterior probabilities of benefits on both outcomes likely suggest a need for further investigations. In the following sections, we will discuss clinical and methodological findings of our study and possible applications of BRMA.

4.5.1 Principal clinical findings

Effects on fractures

Overall, vitamin K maintained a positive trend towards fracture reductions after accounting for its relatively small effects on BMD. The posteriors means of population ORs ranged from 0.7 to 0.9 for vitamin K2 and from 0.5 to 0.9 for vitamin K1. In all BRMAs, uncertainty surrounding the means became smaller, as defined by narrower 95% CrIs. Shrinkages of the predictive distributions around the means of future ORs were even more conspicuous. The 95% CrIs generated in URMAs and those generated in BRMAs included the zero effect and were inconclusive; but, in some cases, a narrower
95% CrI of the BRMA offered more sensible information about the treatment effect. For example, the BRMA-derived 95% CrI around the future OR for vertebral fractures ranged from 0.4 and 1.5, while the corresponding URMA-derived 95% CrI ranged from 0 to 5; the wide URMA-derived 95% CrI allows that in future trials, vitamin K2 can cause a fivefold increase in the risk of fractures or complete risk reduction. Based on this information, we could deduce that either no prior knowledge exists on the efficacy of vitamin K2 on vertebral fractures (not true) or that the current knowledge supports an unrealistic estimate of the vitamin K efficacy.

Effects on BMD

The effects of the K vitamins on BMD remained small and uncertain in BRMA. Similar to the findings of URMA, the pooled MDs were discrepant between the vitamin K preparations and dependent on skeletal sites. Based on the current evidence, the biggest possible increases in BMD were +2.1% at the lumbar spine with vitamin K2 and +1.5% at the femoral neck with vitamin K1. Interestingly, the BRMAs with the greatest increases in BMDs had also the largest shrinkages of 95% CrIs, likely due to large heterogeneity between the combined trials. In contrast, the BRMAs associated with low between-study heterogeneity and small numbers of combined trials generated similar posterior distributions as the corresponding URMAs. Despite the persistently uncertain effects of the K vitamins on BMD in both URMA and BRMA, even the biggest percent increases in mean BMD with the K vitamins are considerably small compared to the effects of pharmacologic therapies (176;244-256).

Probabilities of joint benefits

Our study provided the probabilities of simultaneous benefit on two bone outcomes. In BRMA, congruent with the findings of URMA, vitamin K2 and vitamin K1 showed differential probabilities of benefits between the trabecular and cortical bone sites. Thus, while vitamin K2 benefited more the trabecular bone sites (the odds of any benefit: 9 – 1 and 2 – 1 in current and future trials), vitamin K1 benefited more the cortical bone sites
(the odds of 9 – 1 and 8 – 1 in current and future trials). The probabilities of clinically meaningful benefit on BMD and fractures were lower than 50%. These relatively small probabilities can be explained by the fact that the 95% CrIs around the pooled estimates were wide and included the zero effect; also, the definition of clinically meaningful benefit of 20% reduction in odds of fractures may be overly conservative for non-pharmacological therapies.

4.5.2 Direction of the vitamin K treatment effect on BMD and fractures

Our results indicated an expected (inverse) direction of the treatment effect on BMD at the lumbar spine and all fractures across all combined trials ($\rho_b = -0.2$): the use of vitamin K2 caused an increase in BMD at the lumbar spine and a reduction of fractures. The BRMA on two binary outcomes also showed an expected and a positive direction of the treatment effect suggesting that vitamin K reduced both vertebral and non-vertebral fractures across all combined trials ($\rho_b = +0.2$).

Although the estimation of the between-study correlation provides some clinically useful insight about the direction of the vitamin K treatment effect, we also showed that this value may depend on the number of pooled trials. We faced a challenge in estimating the between-study correlation in meta-analyses of a very small size. In the vitamin K2 bivariate meta-analyses of 10 trials, the point estimate of the between-study correlation indicated a direction of the treatment effect of vitamin K2 on BMD and fractures ($\rho_b = -0.2$) that was different from the one generated for the 14 bisphosphonate trials (Table A4.3: $\rho_b = -0.03$, 95% CrI: -0.8, 0.8). In the bivariate meta-analyses of 4 trials, the estimate of the between-study correlation was almost the same as the estimate generated from the BRMA of the bisphosphonate trials. Therefore, in the BRMA of a very small size (including less than 5 trials), the estimation depended on the prior and not on the observed data, concealing the true direction of the vitamin K1 treatment effect on BMD and fractures.
4.5.3 Other important findings and relation to other studies

Except in the field of diagnostic studies (133;232;261-264), little empirical research has applied Bayesian BRMA to analyze health outcomes. Thus, we compare our results to the findings of theoretical and simulation-based studies (126-129;134;228;232).

Presence or absence of shrinkage in BRMA-derived posteriors

Our finding regarding the presence or the absence of shifts and shrinkage in the posterior distributions of the pooled mean treatment effect is likely caused by the process of “borrowing strength” and is also related to differences in the estimates of the between-study correlation and differences in the values of the between-study variances.

Research has shown that substantive “borrowing strength” across studies and across outcomes in BRMA can cause the shrinkages of the posterior distributions (127-129;134;232). It occurs because a treatment effect of the first component of a bivariate outcome is estimated by explicit sharing of data (i.e., pooled means, within- and between-study variances) between both components of a bivariate outcome through the between- and within-study covariance (127). The same process of data sharing occurs in the estimation of the second component of a bivariate outcome. In addition, compared to URMA, BRMA involves more studies and has a larger degree of “borrowing strength”; therefore, the standard error of the pooled BRMA estimate is smaller, causing the 95% CrI to be narrower (127-129;134;232). The estimates of the between-study variances are also different between URMA and BRMA. The between-study variances were smaller in our BRMAs (Table 4.5). The BRMA associated with the greatest shift of the posteriors of the pooled treatment effect had the largest estimates of the between-study variance (Tables 4.5). Similar to the findings of other studies (122;127;129), we also showed that the amount of between-study variance can influence the estimate of the between-study correlation (Table 4.6). In addition, Ishiak et al. (228) showed that large variance estimates and a larger estimate of the within-study covariance relative to the between-study covariance is frequently present in small meta-analyses and can cause imprecise and biased estimation of the pooled treatment effect. In contrast, Riley et al. (134)
demonstrated that when the number of studies is small or the within-study variance is large, the between-study correlation is poorly estimated. However, this poor estimation is compensated by upwardly biased estimates of the between-study variance; more importantly, inflation of the between-study variance results in no systematic bias in the pooled estimates and produces no substantive increase in the standard errors (134). Indeed, all our BRMAs were characterized by poor estimation of the between-study correlation most likely caused by overestimation of the between-study variance. In our sensitivity analysis, the pooled estimates of the mean treatment effect were robust to changes of the prior specified on the variance-covariance matrix (Table 4.6).

However, we showed the absence of shrinkage of posterior distributions of the treatment effect in some BRMAs (reference analysis), as compared to the corresponding posteriors of URMA. For example, absence of the shrinkage occurred in the BRMA on the effect of vitamin K1 on BMD at the lumbar spine and fractures that included four homogeneous trials (Table 4.3). In these analyses, the values of the between-study correlation and the between-study covariance were close to zero. One explanation for a lack of the shrinkage may be range restriction or lack of variance on the examined outcomes (Table 4.5) (265). Another explanation could be related to the choice of parameter values specified for the prior on the variance-covariance matrix. In sensitivity analysis on the Wishart prior, we did find the shrinkages of the posteriors of mean treatment effects in current and future studies in all BRMAs (including the one on vitamin K1) when we used a Wishart prior that reflected small between-study heterogeneity on both outcomes (i.e., $\tau_1$ and $\tau_2$ were $<0.03$) (Table 4.6 and Figure 4.3). We showed similar results in another study in which we examined 10 non-informative priors specified on between-study variance and their effects on the outputs of univariate meta-analysis (142). It is possible that in order to produce sensible estimation of uncertainty around the random-effect means and predictions, Bayesian URMA and BRMA that combine a small number of studies need to use informative priors on between-study variance to limit unreasonably large between-study heterogeneity.

There have been some discussions suggesting to abandon the use of BRMA or multivariate meta-analysis when the pooled treatment effects of BRMA and URMA are
almost the same (129). In this case, Nam et al suggested that multivariate extension may contribute little to the analysis because of lack of dependence between the outcomes (129). However, two important arguments arise from the literature to support the conduct of BRMA if the treatment effects were measured on two or more clinically related outcomes. First, Riley et al argued that independence between the outcomes, a rationale for URMA, could be assumed only if the within-study correlations are truly zero; but, this assumption may not be reasonable because within-study correlations are mostly unknown and are rarely published (128). Second, if the effect of a treatment is measured on two or more correlated outcomes then the treatment effect is multivariate, and the assumption regarding a lack of correlation between the treatment effects seems clinically implausible (123).

### Sensitivity analysis: the within-study correlations

In addition to computations of the pooled treatment effect, research has indicated the importance of within-study correlations between the study outcomes because of their role on “borrowing strength” (128;228). Our sensitivity analysis considered a range of clinically plausible values for the within-study correlations as well as the extreme values. We showed robustness of the BRMA estimates to the various values of this parameter (Tables A4.4). Our result agrees with the findings in the literature. Nam et al (129) conducted sensitivity analyses on various priors specified on the within-study correlation and showed robustness of their BRMA estimates to the choice of this prior.

### Estimation of the between-study correlation

Another parameter exclusively estimated by BRMA is the between-study correlation ($\rho_b$). In our analyses, regardless of the type of bivariate outcome, 95% CrIs around the values of $\rho_b$ were wide (Table 4, Figure 1), suggesting its poor estimation (128;228). Estimation of the between-study correlation was likely influenced by the amount of evidence and degree of between-study heterogeneity but not by the type of vitamin K. As previously mentioned, the small (almost zero) between-study correlations ($\rho_b$: -0.01 to -0.03) were
estimated in one set of BRMAs. These analyses included a small dataset of homogeneous trials with one trial reporting completely treatment effects on both outcomes (vitamin K1), or included a dataset with no study reporting completely treatment effects on both outcomes (vitamin K2: femoral neck). Consequently, the estimation of the between-study correlation was likely driven by the prior derived from the bisphosphonate trials ($\rho_b = -0.02, 95\%\text{CrI}: -0.8 \text{ to } 0.8$, Appendix: Table A4.3)

Poor estimation of the between-study correlation in our BRMAs agrees with the findings in the literature (122;129;134). Jackson (122) demonstrated that the main statistical difficulty of BRMA is related to the imprecise estimation of the variance-covariance or precision matrix (denoted as $\Omega$). One of the proposed solutions was to use Bayesian methods and assign a prior on $\Omega$. A most commonly specified prior on $\Omega$ is an inverse non-informative Wishart prior (232;233). However, research has shown that non-informative priors on the precision matrix or on the between-study variance should be carefully specified as they can influence the outputs of the Bayesian meta-analysis (141;142;232;233). In our sensitivity analyses, imposing large or small between-study heterogeneity on the Wishart prior had no effect on the point estimates of pooled treatment effects or the overall conclusions of BRMAs (Table 4.6); but, it had affected the estimate of the between-study correlation and the 95\%CrIs around the predictions.

Xing et al (266) examined the impact of non-informative priors specified on the precision matrix in a Bayesian bivariate meta-analysis of diagnostic outcomes (i.e., sensitivity and specificity). They showed no changes in the point estimates of sensitivity and specificity; however, they found important differences in the point estimates of the between-study correlation resulting from different priors including an inverse Wishart distribution. The differences were more pronounced when the sample size was small (25 per group) (266).

In addition, our study employed a relatively novel approach and complemented the estimation of the precision matrix $\Omega$ (122). In reference analysis, we “borrowed strength” from the data of 14 homogeneous trials, while in sensitivity analysis, we used the data of three heterogeneous vitamin D trials. With the vitamin D data, our results changed as the estimates of BRMAs became similar to those of URMAs. This finding indicates that the prior on between-study correlation needs to be derived from a larger
number of trials; it also endorses future research on the use of informative priors on between-study correlation in BRMAs that pool small numbers of trials.

4.5.4 Implications and further applications

The results of our study support the idea that BRMA may be more advantageous than URMA particularly in cases involving considerable uncertainties around the pooled treatment effect. In the following section, we will present three important applications of BRMA.

Through estimation of the between-study correlation (134), our study shows the directions of the underlying true treatment effects in two outcomes across trials. In situations where clinical uncertainty is driven by the opposing effects of treatment on surrogate and the most important endpoints, information on the between-study correlation is valuable. For instance, based on the findings of URMAs, a negligible effect of vitamin K on BMD does not align well with its large effect on fractures. Based on the findings of BRMA, vitamin K may increase BMD and decrease the odds of fractures, which is an expected direction of changes in two major bone outcomes, shown for many other drugs used for treating osteoporosis (176;244-256).

Next, Bayesian BRMA can be used to forecast the effect of treatment on a bivariate outcome in situations when trials report either of the two endpoints, assuming that unreported outcomes are missing at random and that the treatment estimates are correlated (122). This application of BRMA has been shown in our analyses of the effect of vitamin K2 on BMD at the femoral neck and non-vertebral fractures where no trials reported both endpoints. Our BRMA analyses are conceptually similar to other bivariate meta-analyses that modeled differences in treatment effects on surrogate (intermediate) and clinical outcomes. For example, the development of AIDS or death and CD4 cell count were jointly modeled to examine treatment effects of HIV drugs; amplification of the MYCN oncogene and partial deletion of chromosome 1p were simultaneously examined because they are highly correlated prognostic factors of a poor survival in children with neuroblastoma (128;267;268). BMD is an intermediate outcome often used in bone drug trials to evaluate the effect of a treatment; in clinical practice,
changes in BMD over time are examined to determine the progression of osteoporosis. However, two important concerns are related to a conduct of BRMA on surrogate and true clinical outcomes (267;268). First, compared to using solely data measured on true clinical outcomes, additional use of the data on surrogate outcomes decreases the precision of the estimated pooled treatment effect on the true outcomes (268). The amount of between-study variation in the true outcomes affects the precision of the pooled estimate even when there is a strong correlation between the true and surrogate outcomes. Large between-study variation in the true outcome often leads to imprecise estimation. Therefore, to generate precise estimates of the pooled treatment effect on the true outcomes, and make use of data measured on strongly correlated surrogates, between-study variation in the true outcomes needs to be small and a number of pooled studies needs to be large (268). Second, since the changes in two outcomes are often measured at different time points, an intermediate outcome needs to be considered as a “concurrent outcome” (267): a treatment effect on an intermediate (surrogate) outcome over time should correlate with the effect on the corresponding true clinical outcome. Since information on the within-study correlations may not be available, clinical judgment needs to be combined with sensitivity analysis. Therefore, more theoretical and empirical research is required to examine validity of BRMA on surrogate outcomes when the number of combined trials is small. This kind of research may have some implications on policy-making and on investments in future funding: the results of BRMA on surrogate outcomes may provide valid justifications for conducting very expansive trials on rare but clinically important outcomes.

Lastly, a potentially promising application of Bayesian BRMA is in the areas of cost-effectiveness analyses and value of information analyses. These economic methods are used to select strategies with the highest expected values (returns) and to determine priorities for future research through the expected value of perfect information (EVPI) (99;101;102;114;226;269). It has been suggested that the prediction of treatment effect represents a better estimate than the population treatment effect as predictive distributions include uncertainties around both the population treatment effect and the estimate of between-study heterogeneity (80;119); as such, the use of predictive distributions has been recommended in economic evaluations (114;118;226). Our economic study
presented in Chapter 2 identified the efficacies of the K vitamins as key determinants of the incremental cost-effectiveness of vitamin K for the prevention of fractures (196). In the current study, we further explored uncertainty in the incremental cost-effectiveness of the K vitamins and used the population and future ORs of BRMA and URMA to populate the economic model (Appendix: Tables A4.5). The new efficacy estimates particularly affected the incremental cost-effectiveness of vitamin K2 (Tables 4.7 and 4.8). Thus, if the future ORs of BRMA were used, lifetime supplementation with vitamin K2, vitamin D and calcium over vitamin D and calcium alone was not a cost-effective intervention at commonly used thresholds. In contrast, vitamin K1 given with vitamin D and calcium over vitamin D with calcium alone became a cost-saving strategy. Additionally, compared to the results of the original analysis (196), the probability of cost-effectiveness of lifetime supplementation with vitamin K2, vitamin D and calcium over vitamin D and calcium alone considerably decreased: it was 33.8% at a threshold of $50,000/QALY (originally 94.7%) and 49.5% at a threshold of $100,000/QALY (originally 100%) (Appendix: Figure A4.1). In the new analysis, the probability of cost-effectiveness of lifetime supplementation with vitamin K1, vitamin D and calcium over vitamin D and calcium alone remained over 80% at the willingness-to-pay thresholds over $50,000/QALY (Appendix: Figure A4.2). However, despite these changes, the estimates of the population EVPI were still high (approximately $124 billion for vitamin K2 and $94 billion for vitamin K1), indicating remaining uncertainties around the efficacies of the K vitamins and confirming the need for further research.

4.5.5 Strengths and limitations

We used complex Bayesian BRMA approaches, which included all available data and accounted for correlations between treatment effects measured on BMD and fractures, to evaluate the efficacy and probabilities of benefits of the K vitamins for the prevention of bone loss and fractures in postmenopausal women. Our study demonstrated a pragmatic role of Bayesian BRMA to forecast the treatment effect on unmeasured outcome by using information about its effect on the measured outcome. We also demonstrated a novel statistical method to improve the estimation of the between-study correlation. Finally, we showed an application of the estimates of BRMA in economic models.
However, our study was limited in several ways. While some limitations are connected to the specifics of research on vitamin K, they most closely reflect recognized issues pertinent to meta-analysis of a small size (122;129). First, we combined data of all available trials that were characterized by various methodological quality and low power to detect small but clinically important effects on fractures. Thus, with a small sample size and a large amount of missing data, caution must be applied regarding the BRMA estimates of the efficacies of the K vitamins. Nonetheless, this study was undertaken to determine whether uncertainty around the efficacy of vitamin K changed after accounting for the within- and between-study correlations between treatment effects measured on BMD and fractures. Also, its aim was to validate the conclusions of our previous economic evaluation (196) and URMAs regarding the gap in knowledge and the need for a future trial on vitamin K and fractures. In the new CEAs, we used the estimates of the vitamin K treatment effects on fractures adjusted for the small effects on BMD to better inform input parameters related to the efficacies of the K vitamins on fractures. The BRMA-derived population and future ORs were based on larger, updated sets of pooled trials; however, the conclusions of our new CEAs should be interpreted with caution because our Markov microsimulation model was a fracture incidence-based model that did not account for changes in BMD over time. Given the small effects of vitamin K2, vitamin D and calcium on BMD, we could speculate that the results of another CEA based on modeling changes in both BMD and fractures over time would not produce drastically different conclusions from our current study. Second, we did not verify the underlying normality assumption of BRMA – the assumption of a linear relationship between studies. This assumption has been rarely tested in other BRMAs. Jackson et al (122;270) indicated that non-linear relationships between combined studies (i.e., violation of multivariate normality) likely affect borrowing of the strength, but also pointed out that the linearity assumption is hard to verify in multivariate meta-analyses including small numbers of trials and consequently, urged methodologists to conduct further research on this issue. Third, we assumed that the outcomes were missing at random – another underlying assumption of BRMA. Given missingness at random (MAR), multivariate methods are recommended for dealing with dissemination and outcome reporting bias (122;128;129;134;271). We argue that due to feasibility issues or due to
high costs of fracture trials, MAR was unlikely violated in our study (i.e., missing treatment effects on fracture outcomes were not associated with changes in mean BMDs and vice versa: log odds-ratios of fractures were not associated with missing treatment effects on BMD). Fourth, variability in reporting of BMD and fracture outcomes is cause for concern. Most often, journals do not require reporting of all outcomes in the same manner: it is left to investigators to choose which outcome data will be fully presented in tables and which will be presented graphically; reporting of the within-study correlations is not a standard. In our analyses, few studies reported complete outcome data; no trials reported within-study correlations. Consequently, imputation of variance data was performed in many analyses. The influence of this measurement bias may not be as large because our sensitivity analyses showed that the results were robust to a wide range of values specified for the within-study correlations. Also, changes of the estimates of between-study variance did not affect our conclusions. Nevertheless, better outcome reporting can help improve confidence in the validity of study conclusions. Next, we showed in the analyses with a large amount of missing endpoints that estimation of the between-study correlation could be improved by “borrowing strength” from data of other bone-related studies (given that expected correlations and directions of effects are similar). In sensitivity analysis, we found that “borrowing strength” from a small number of heterogeneous vitamin D trials led to highly inconclusive estimates of the treatment effect. Therefore, our approach of resolving statistical difficulties regarding estimation of the precision matrix deserves further validation in empirical or simulation-based BRMAs. In addition, we did not use meta-regression within BRMA to explore changes in the bivariate treatment effects of the K vitamins after adjusting for important covariates. It is possible that the bivariate treatment effects of vitamin K2 on BMD and fractures would be dependent on the characteristics of the study population. Lastly, we should interpret the results on posterior probabilities of clinically important benefits on both outcomes wisely because of lack of knowledge regarding an acceptable benefit threshold from non-pharmacological treatments.
4.5.6 Conclusions

Our study makes five noteworthy contributions to the current literature on vitamin K and Bayesian evidence synthesis. First, to our knowledge, this is the first study in the area of osteoporosis that has applied Bayesian BRMA methods. We showed several advantages of Bayesian BRMA over separate univariate meta-analyses. BRMA included all available data, accounted for within and between-study correlations and more precisely estimated the true treatment effect of vitamin K on BMD and fractures. Second, our research increases understanding of the challenges and potentials of Bayesian BRMA in situations when the number of pooled studies is small. Third, our study confirms uncertainties around the efficacies of the K vitamins on fractures. Fourth, it demonstrates differential probabilities of joint benefits of the K vitamins on the cortical and trabecular bone skeletal sites and indicates the need for further research in this area. Finally, we demonstrate that bivariate meta-analysis is a useful tool to capture complex directions of treatment effects and, as such, may be a valuable method to synthesize evidence. Further research needs to validate the use of Bayesian bivariate and multivariate meta-analyses in the area of surrogate outcomes. Future studies also need to evaluate accuracy of the predictions of the true treatment effect resulting from Bayesian bivariate or multivariate meta-analysis of a small size.

4.6 Acknowledgments

The results of this study were presented among the top-rank abstracts (oral presentation) at the 34th SMDM annual meeting, Phoenix, AZ, USA: October 17-20, 2012.
Chapter 5
Discussion and conclusions

5. Discussion

5.1 Contributions to the literature

There has been substantive interest in the vitamin K effect on bone, with approximately 20 RCTs assessing the effects of vitamin K2 and vitamin K1 on BMD and fractures in postmenopausal women (59-65;71;168;170;171;214-221). The trials including fracture endpoints showed large beneficial effects of the K vitamins in contrast to the trials assessing BMD. This thesis research included three studies and was conducted to synthesize the current evidence and to examine whether the K vitamins can be recommended for the primary prevention of osteoporosis and fractures in postmenopausal women. In the section below, including Tables 5.1 and 5.2, we summarize the most important findings:

1. **Study 1** was a cost-effectiveness analysis that compared no supplementation to lifetime supplementation with vitamin D3 and calcium alone and to lifetime supplementation with vitamin K2 (or vitamin K1), vitamin D3 and calcium (196). The incremental cost-effectiveness ratios associated with the vitamin K strategies were much less than $50,000/QALY and the probabilities of cost-effectiveness were 95% (vitamin K2) and 80% (vitamin K1) at a willingness-to-pay threshold of $50,000/QALY (Table 5.1). In sensitivity analyses, the efficacies of the K vitamins were identified as key drivers of the cost-effectiveness results. The incremental cost-effectiveness of the K vitamins was associated with high costs of making wrong decisions.

2. **Study 2** comprised of a systematic review of the literature (1947-December 2012), Bayesian and classical univariate random-effects meta-analyses (URMAs) and meta-regressions. In general, the number of meta-analyzed trials was small (Table 5.2). Compared to the URMAs of the vitamin K1 trials, the URMAs of the vitamin K2 trials
were highly heterogeneous. We found small but differential effects of the K vitamins on BMD. The probabilities of any increase or an important increase in BMD ranged widely and were dependent on the vitamin K preparation and the skeletal site (Table 5.1). For example, vitamin K2 benefited the lumbar spine BMD with relatively high probabilities in contrast to vitamin K1. While the evidence of the effect of vitamin K1 on fractures was insufficient, the evidence on the effect of vitamin K2 was positive but inconclusive. Vitamin K2 benefited vertebral fractures and non-vertebral fractures with the probabilities $\geq 72\%$ and $\geq 62\%$, respectively.

3. Study 3 was the first study to use Bayesian bivariate random-effects meta-analysis (BRMA) to capture joint effects of the K vitamins on BMD and fractures. An important methodological finding was that the predictive posteriors of the true treatment effect in future trials shrank substantially in BRMA; in comparison to URMA, the BRMA-derived widths of 95\% CrIs decreased up to fivefold (Table 5.1). The BRMA-derived estimates of the treatment effect were more precise. A direction of the treatment effect on BMD and fractures across all studies, based on the mean value of between-study correlation, was either negative (e.g., $-0.2$: the vitamin K2 effect on lumbar spine BMD and all fractures) or zero. Similar to the results of URMA, the BRMA-derived probabilities of any and important benefits on both outcomes were different between two K vitamins, and were dependent on the skeletal site. For example, vitamin K2 benefited both vertebral fractures and lumbar spine BMD with at least two-three times greater probabilities than vitamin K1. Vitamin K1 benefited non-vertebral fractures and femoral neck BMD with two-five times greater probabilities than vitamin K2.

4. The last important finding is that the incremental cost-effectiveness of the K vitamins depended on the method used to estimate their efficacies. When the population odds ratios of URMA were used to populate a model, the vitamin K2 strategy was still cost-effective at a threshold of $50,000/QALY. However, it stopped representing “good value for money” when the population odds ratios of BRMA were used, as the ICER steeply increased from $21,500/QALY to $74,800/QALY (Table 5.1). Using the future odds ratios of BRMA, the vitamin K2 strategy was not cost-effective at a threshold of $100,000/QALY, while the vitamin K1 strategy was cost-saving. This difference in
incremental cost-effectiveness between the two K strategies may be explained by the fact that in future trials, vitamin K1 was associated with slightly better efficacy estimates than vitamin K2 (future odds ratios [K2]: 0.8-0.9, 95%CrIs: 0.4-1.6; future odds ratios [K1]: 0.6, 95%CrIs: 0.1-1.9). The unfavorable incremental cost-effectiveness of vitamin K2 partially agrees with the finding that the future odds of joint benefits on BMD and fractures were lower with vitamin K2 than with vitamin K1 (vertebral fractures and lumbar spine BMD: 67% [K2], 33% [K1]; non-vertebral fractures and femoral neck BMD: 43% [K2]; 75% [K1]). However, the population expected values of perfect information (EVPI) remained large in all analyses, indicating persistent decision uncertainty regarding adoption of the K vitamins into routine clinical practice.
Table 5.1. The most important results of the three thesis studies

<table>
<thead>
<tr>
<th>IMPORTANT RESULTS</th>
<th>Study 1</th>
<th>Study 2 (URMA)</th>
<th>Study 3 (BRMA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FRACTURES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effects on odds of fractures (ORs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequentist population OR (95% CI): VF</td>
<td>0.4 (0.3-0.7)§</td>
<td>0.5 (0.1-1.5)§</td>
<td>NA</td>
</tr>
<tr>
<td>Bayesian population OR (95% CrI): VF and bivariate outcomes a,b</td>
<td>NA</td>
<td>NA</td>
<td>0.8 (0.5-1.1) ab</td>
</tr>
<tr>
<td>Bayesian predictive OR (95% CrI): VF and bivariate outcomes a,b</td>
<td>NA</td>
<td>NA</td>
<td>1.2 (0.1-5.2)</td>
</tr>
<tr>
<td>Frequentist population OR (95% CI): non VF</td>
<td>0.3 (0.1-1.7)§</td>
<td>0.3 (0.0-8.4)§</td>
<td>0.8 (0.6-1.3)</td>
</tr>
<tr>
<td>Bayesian population OR (95% CrI): non VF and bivariate outcomes c,d</td>
<td>NA</td>
<td>NA</td>
<td>0.5 (0.1-1.3)</td>
</tr>
<tr>
<td>Bayesian predictive OR (95% CrI): non VF and bivariate outcomes c,d</td>
<td>NA</td>
<td>NA</td>
<td>1.0 (0.0-5.5)</td>
</tr>
<tr>
<td>Probabilities of benefits (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(benefit)/ P(important benefit) – current studies – VF or bivariate fracture outcome j</td>
<td>NA</td>
<td>NA</td>
<td>89 / 75</td>
</tr>
<tr>
<td>P(benefit)/ P(important benefit) – future studies – VF or bivariate fracture outcomes j</td>
<td>NA</td>
<td>NA</td>
<td>72 / 62</td>
</tr>
<tr>
<td>P(benefit)/ P(important benefit) – current studies – non VF or bivariate fracture outcomes j</td>
<td>NA</td>
<td>NA</td>
<td>94 / 87</td>
</tr>
<tr>
<td>P(benefit)/ P(important benefit) – future studies – non VF or bivariate fracture outcomes j</td>
<td>NA</td>
<td>NA</td>
<td>78 / 72</td>
</tr>
<tr>
<td><strong>BMD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effects on percentage mean changes in BMD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequentist MD (95% CI): BMD at the lumbar spine</td>
<td>NA</td>
<td>NA</td>
<td>1.2 (0.1-2.2)</td>
</tr>
<tr>
<td>Bayesian MD (95% CrI): BMD at the lumbar spine and bivariate outcome e</td>
<td>NA</td>
<td>NA</td>
<td>1.2 (0.0-2.5)</td>
</tr>
<tr>
<td>Bayesian predictive MD: BMD at the lumbar spine and bivariate outcome e</td>
<td>NA</td>
<td>NA</td>
<td>1.2 (-2.3-4.8)</td>
</tr>
<tr>
<td>Frequentist MD (95% CI): BMD at the femoral neck</td>
<td>NA</td>
<td>NA</td>
<td>0.1 (-0.3-0.6)</td>
</tr>
<tr>
<td>Bayesian MD (95% CrI): BMD at the femoral neck and bivariate outcome f</td>
<td>NA</td>
<td>NA</td>
<td>0.1 (-0.7-0.9)</td>
</tr>
</tbody>
</table>

Note: § indicates significance, a,b,c,d,e,f indicate different study populations.
**IMPORTANT RESULTS**

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2 (URMA)</th>
<th>Study 3 (BRMA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayesian predictive MD: BMD at the femoral neck and bivariate outcome</td>
<td>NA</td>
<td>NA</td>
<td>0.1 (-1.1-1.3)</td>
</tr>
<tr>
<td>Probabilities of benefits (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(benefit)/ P(important benefit) – current studies – BMD at the lumbar spine or bivariate BMD-fracture outcome</td>
<td>NA</td>
<td>NA</td>
<td>97 / 88</td>
</tr>
<tr>
<td>P(benefit)/ P(important benefit) – future studies – BMD at the lumbar spine or bivariate BMD-fracture outcome</td>
<td>NA</td>
<td>NA</td>
<td>77 / 67</td>
</tr>
<tr>
<td>P(benefit)/ P(important benefit) – current studies – BMD at the femoral neck or bivariate BMD-fracture outcome</td>
<td>NA</td>
<td>NA</td>
<td>68 / 13</td>
</tr>
<tr>
<td>P(benefit)/ P(important benefit) – future studies – BMD at the femoral neck or bivariate BMD-fracture outcome</td>
<td>NA</td>
<td>NA</td>
<td>66 / 16</td>
</tr>
</tbody>
</table>

**COST-EFFECTIVENESS**

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2 (URMA)</th>
<th>Study 3 (BRMA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental cost-effectiveness ratio (ICER), $/QALY</td>
<td>&lt; 20,000</td>
<td>&lt; 10,000</td>
<td>&gt; 20,000</td>
</tr>
<tr>
<td>Probability of cost-effectiveness †, %</td>
<td>95</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>Expected value of perfect information per person (EVPI) †, $</td>
<td>1,110</td>
<td>15,960</td>
<td>4,750</td>
</tr>
<tr>
<td>Population expected value of perfect information †, $ in billions</td>
<td>29</td>
<td>415</td>
<td>124</td>
</tr>
</tbody>
</table>

URMA denotes univariate random-effects meta-analysis; BRMA denotes bivariate random-effects meta-analysis; OR denotes odds ratio; CI denotes confidence interval; CrI denotes credible interval; VF denotes vertebral fractures, non VF denotes non-vertebral fractures; P(benefit) denotes the probability of any benefit (i.e., OR ≤ 1 or percentage mean difference > 0); P(important benefit) denotes the probability of showing OR = 0.80 or the percentage mean difference = 1%; MD denotes the percentage mean difference in BMD; BMD denotes bone mineral density; † Data based on the literature; ¹ hip fractures; ² wrist fractures; ³ bivariate outcome: VF adjusted for LS BMD; ⁴ bivariate outcome: VF adjusted for non VF; ⁵ bivariate outcome: non VF adjusted for FN BMD; ⁶ bivariate outcome: non VF adjusted for VF; ⁷ bivariate outcome: LS BMD adjusted for VF; ⁸ bivariate outcome: FN BMD adjusted for non VF; ⁹ probability of benefit (important benefit) in both outcomes (i.e., bivariate outcome); NA= not applicable; † willingness-to-pay of $50,000/QALY.
Table 5.2. Additional important characteristics and findings of the univariate and bivariate meta-analyses

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of pooled studies</td>
<td>8 4 2 4 4 1 10 a 6 b</td>
<td>10 a 2 a 6 b</td>
<td>4 4</td>
<td>4 4</td>
<td>4 1</td>
<td>4 4</td>
<td></td>
</tr>
<tr>
<td>Number of studies reporting completely both outcomes</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
<td>NA NA</td>
<td></td>
</tr>
<tr>
<td>Sample</td>
<td>1332 1011 659 872</td>
<td>4384 440</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-study heterogeneity§</td>
<td>large small large large</td>
<td>large a small b large</td>
<td>large a small b large</td>
<td>large a small b large</td>
<td>large a small b large</td>
<td>large a small b large</td>
<td></td>
</tr>
<tr>
<td>Between-study standard deviation: τ (95% CrI)</td>
<td>0.9 (0.3-1.7)</td>
<td>0.4 (0.1-0.8)</td>
<td>1.2 (0.3-1.7)</td>
<td>1.3 (0.3-2.1)</td>
<td>1.2 (0.3-1.7) a</td>
<td>0.3 (0.0-1.5) b</td>
<td>NA</td>
</tr>
<tr>
<td>Between-study correlation: ρb (95% CrI)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Risk of bias (across studies)</td>
<td>unclear high unclear and low high unclear and low high</td>
<td>unclear and low uncertain and low high uncertain and low high</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

URMA denotes univariate random-effects meta-analysis; BRMA denotes bivariate random-effects meta-analysis; LS denotes lumbar spine; FN denotes femoral neck; VF denotes vertebral fractures, non VF denotes non-vertebral fractures; § Qualitative statement (small vs. large) was based on the mean between-study standard deviation (τ), where τ<0.5 is assumed small heterogeneity (138); NA= not applicable; CrI denotes credible interval.
5.1.1 Putting it into perspective

In the following section, our overall findings will be discussed in context of the current clinical and methodological evidence.

Controversies of Bayesian estimates: Highly uncertain efficacies combined with potentially high probabilities of benefits

The effects of the K vitamins were small on BMD at any skeletal site. A mean percent increase in BMD ranged from zero to one percent in both current and future trials. In most analyses, these estimates were associated with wide 95% credible intervals crossing zero. Based on the current data, the probabilities of any benefit on single or on both bone outcomes were high at the trabecular bone sites for vitamin K2 and at the cortical bone sites for vitamin K1. However, the corresponding probabilities of clinically important benefits decreased almost by half. These differences can be explained by the fact that the pooled random-effects means were quite close to our definitions of clinically important benefit. Also, the pooled estimates were associated with the wide and inconclusive credible intervals, with the upper limits that indicated slightly greater benefits than the benefits assumed as clinically important.

Our results pose two interconnected questions for which the answers are yet to be determined. The first question relates to a threshold regarding an important clinical change that could be used for the efficacy of vitamin K on fractures. It is still unclear whether expected efficacies of the K vitamins should equal to those of pharmacological therapies or to that of vitamin D with calcium. The second question relates to a value of Bayesian probability of benefit that should be defined as clinically important. This threshold is particularly valuable for the interpretation of the probabilities of benefits of the K vitamins in future trials because it could be used to justify the expectations of potentially positive results in a new trial. To understand Bayesian probabilities better, the analyst can transform the probabilities into a ratio of odds to show how many times the alternative hypothesis is as likely as the null hypothesis. Most liberally, the ratio that
equals to the posterior odds greater than 1 (probabilities of benefit >50%) might indicate the lowest acceptable benefit of the treatment (145). In the context of our study, if we assume that the probability greater than 50% represents an acceptable threshold of benefit, then a 67% probability that vitamin K2 will benefit vertebral fractures and a 75% probability that vitamin K1 will benefit non-vertebral fractures seem high, and in favor of conducting a new trial.

**Differential effects of the K vitamins on the trabecular and cortical bone or on overall bone quality?**

Despite the small effects of the K vitamins on BMD, it is worth discussing a possibility of their differential effects on bone (at various skeletal sites). In both URMA and BRMA, we found that vitamin K2 benefited more BMD at the lumbar spine than BMD at the femoral neck. We showed the opposite results for vitamin K1. In addition, Fang et al (57) pooled BMD data from mixed populations and also found a differential effect of the K vitamins on trabecular and cortical bone. Differences in the effects between the K vitamins on trabecular and cortical bone may be explained by the findings of *in vitro* and *in vivo* studies.

*In vitro* studies showed differences in the effects of the K vitamins on bone metabolism: both vitamins affected bone formation, but vitamin K2 more strongly inhibited osteoclastogenesis and prevented bone resorption compared to vitamin K1 (272). While vitamin K2 was shown to affect the osteoprotegerin (OPG)/ NF-kB ligand (RANKL) pathway through its side chain (geranyl-geranyl) and to force osteoclasts to undergo apoptosis (273-275), vitamin K1 inhibited osteoclastogenesis but did not lead osteoclasts to apoptosis (273).

In *in vivo* animal studies, vitamin K2 benefited mostly trabecular bone, bone strength and bone quality (276-280), while vitamin K1 benefited mostly cortical bone (281). In study by Tomiuga et al (276), vitamin K2 was shown to increase bone strength of vertebrae but not of femurs. Iwamoto et al also showed that vitamin K2 affected more strongly trabecular bone than cortical bone (277). Vitamin K2 was shown to increase trabecular
number (278) and trabecular thickness (282). Mawatari et al (279) showed that MK-4 (vitamin K2) significantly increased trabecular bone volume, trabecular dimension and connectivity. In 2012, Matsumoto et al used micro-computed tomography to show that MK-4 affects bone quality (280). In rats supplemented with MK-4, trabecular volume fraction and trabecular thickness significantly increased; MK-4 did not affect the cortical pore structure or mineralization, but it significantly increased mineral crystallinity, collagen maturity and hardness of the anterior and posterior cortices (280). A few studies in animals directly compared the effects of vitamin K1 and vitamin K2 on trabecular and cortical bone. In 2011, Sogabe et al (281) compared the long-term addition of phylloquinone (PK) or MK-4 to a control diet and their effects on BMD and bone strength parameters. At three months, in rats on a diet with PK, BMD of the femur significantly increased while in rats on a diet with MK-4, BMD did not change. However, the diet with MK-4 significantly increased bone strength parameters (i.e., the minimum cross-sectional moment of inertia and the polar moment of inertia) as well as the femoral bone parameters (the width, dry weight and ash weight, and cortical, cancellous, trabecular, and total bone mineral contents). In summary, vitamin K2 may affect both trabecular and cortical parts of the bone, but the effects may be confirmed only through measuring bone quality parameters (not BMD).

In addition, differential effects of vitamin K2 and vitamin K1 on bone may exist due to differences in genetics, lifestyle or dietary factors between Asian and Caucasian populations (283;284). It has been shown that as compared to Caucasians, Japanese and Chinese postmenopausal women have greater declines in BMD (283) and lower trabecular density (284), but also have higher cortical thickness (284).

“Fragile” incremental cost-effectiveness of the K vitamins

This is the first study to show important fluctuations of the cost-effectiveness outcomes with the use of Bayesian predictions. Riley et al. (119) and Higgins et al. (80) emphasized that prediction intervals better represent uncertainty around the true treatment effect as they account for the uncertainty around the pooled estimate, the estimate of
between-study variance and the uncertainty around between-study variance. Spiegelhalter et al. (115) and Ades et al. (118) proposed to use the predictive distribution in decision-analytic models instead of the random-effects mean to account for all variation around the true treatment effect.

Despite the fluctuations of the ICER, our estimates of the population EVPI remained unchanged and high (approximately $124 billion). This finding leads to another more complex issue related to the allocation of scarce healthcare resources. The ICER is a tool that is most often used to decide whether a new clinical strategy is cost-effective and whether it should be adopted (as compared to the chosen willingness-to-pay threshold) (89). However, if this decision is based solely on a value of the ICER, the costs of making the wrong decision remain unknown (97;101). In our studies, large values of the population EVPI indicate that the cost of making a wrong decision is high. For example, if the total direct and indirect costs of osteoporotic fractures in Canada are around $3.5 billion and if these costs account for 1.3% of Canada’s health expenditures (10), then our estimates of the population EVPI of $124 billion is close to the half of Canada’s health expenditures (approximately $270 billion). We could also compare the value of the EVP with a cost of a new RCT, powered to detect clinically important difference. If we assume that an incidence of fractures in untreated patients will be 10% and that vitamin K will reduce fractures by 20% (i.e., the efficacy of vitamin D with calcium), and also, expect a loss to follow up of 10% and 80% compliance, we would need 5633 patients per group to detect the effect (alpha=0.05 and power= 0.8). Assuming that a reasonable cost for this trial is 2 million, then the approximate EVPI per person will be $178 and the corresponding approximate value for the population EVPI will be $4.6 billion. This value is far below our estimated maximum expected cost of additional research (population EVPI) of $124 billion at a willingness to pay threshold of $50,000/QALY. Our model would approach the population EVPI of $4.2 billion at a willingness-to-pay threshold of $8,000/QALY; thus, if one QALY is deemed worth only $8,000, then the new research would not be required. However, in most economic evaluations, the thresholds of $50,000/ QALY and $100,000/QALY are used; at these thresholds, the corresponding population EVPI is $124 billion and $378 billion. In summary, our research confirms
that resource allocation should not be solely based on the ICER, but should be justified through several analyses including value of information analyses.

Another insight about a possible relation between the efficacy, the ICER and the EVPI evolves from our bivariate meta-analysis. For example, populating a model with the more precisely estimated future ORs of BRMA led to more meaningful cost-effectiveness estimates and a stronger positive correlation between the ICER and the population EVPI. The ICER was >$100,000/QALY with the BRMA-derived future ORs and it was $21,500/QALY with the URMA-derived population ORs, while the population EVPIs were $124 billion in both analyses. Large values of both economic statistics, based on the estimates of the bivariate meta-analyses, were consistent regarding a recommendation against adoption of vitamin K2 into routine clinical practice.

Changes in the cost-effectiveness of the vitamin K1 strategy also deserve some discussion. The vitamin K1 strategy became cost-saving when the BRMA-derived efficacy estimates were used to populate an economic model. This may be explained by substantial changes of the OR distribution. For example, a 95% credible interval of the OR associated with the effect of vitamin K1 on hip fractures ranged from 0.01 to 8.4 in the original study (196); in the BRMA, the interval narrowed down to 0.2 to 1.3 (assuming similarity of the ORs for hip and non-vertebral fractures). The population EVPI declined approximately 4.5 times from the original $415 billion to $93 billion, but it still remained high.

Bayesian BRMA: A promising method

In addition to the clinical aspect of our research, we made important methodological contributions to the literature. The case of vitamin K increased our understanding about the performance of BRMA in the meta-analysis of a small number of trials. Our findings agree with the findings of theoretical studies (127;129): as compared to the posteriors of URMA, most posteriors of BRMA were narrower. The BRMA-derived predictive distributions associated with the effect of vitamin K2 shrunk the most.
However, given the complexity of modeling in BRMA, it may be important to discuss whether there is a situation when conducting URMA could be more advantageous. This question regarding doing “BRMA vs. URMA” resembles the one regarding doing “random-effects vs. fixed-effects meta-analysis”. Random-effects meta-analysis is considered more advantageous over fixed-effects meta-analysis for at least three reasons. First, in case of homogeneity, both types of meta-analyses might generate similar results, and second, random-effects meta-analysis is the only analysis that can be used to generate a prediction of the true treatment effect in a future trial, which is according to some authors an ultimate goal of meta-analysis (80;119). Lastly, the Bayesian approach to bivariate or multivariate meta-analysis is the only valid way to estimate the probabilities of joint benefits on two or more outcomes. Thus, if a treatment effect is measured on two or more correlated outcomes, then all data should be utilized so that the treatment effect could be analyzed as multivariate. Whether between-study variance plays an important role in multivariate meta-analysis and whether univariate and multivariate meta-analyses will generate similar results in the case of between-study homogeneity is still to be answered.

5.2 Strengths and limitations

To explore uncertainties in the efficacies of the K vitamins on fractures, we used novel and advanced methods of decision-analytic modeling and evidence synthesis. However, all three studies were retrospective analyses of previously collected data and are associated with two important limitations (the limitations of each study were previously elaborated in chapters 2-4).

The first major weakness is related to methodological shortcomings of the combined trials. The fracture evidence was restricted to a small sample of underpowered trials of variable methodological quality. The designs of vitamin K2 and vitamin K1 trials differed substantially in study populations, most likely answering distinct research questions. A risk of within-study bias was high or unclear in most vitamin K2 trials. Due to these methodological limitations, our analyses were stratified by the type of
vitamin K, in contrast to the 2011 meta-analysis by Fang et al (57). Indirect (mixed) treatment comparisons also seemed inappropriate because of high heterogeneity between the study populations (285).

The second important limitation is related to measurement bias or measurement error that affected the analyses in four different ways. First, variability in reporting of BMD and fracture data led to either their approximation from the original (published) graphs (e.g., chapter 3, Appendix 2: Figure A3.3), or their imputation. In comparison to other BMD outcomes (e.g., mean changes in areal BMD), the mean percent change in BMD was the most completely reported outcome in individual trials and thus, was pooled in the meta-analyses. Second, incomplete data reporting was a serious cause for concern in BRMA modeling: only two vitamin K2 trials (168;170;216) and one vitamin K1 trial (60) reported both BMD and fracture endpoints and not a single trial reported within-study correlations. Thus, for each missing endpoint, we approximated large amounts of data pertinent to variances and effect sizes. However, theoretical research (134) and our sensitivity analyses showed that different estimates of the within and between-study variance caused no changes in the study conclusions. Third, vitamin K trials favored measuring the treatment effect on an intermediate outcome (BMD); this led to overall lack of trials measuring the effect of vitamin K on fractures or on both endpoints. Consequently, modeling and estimation of the between-study correlation in BRMA were constrained by the assumption that the between-study correlations between the bisphosphonate and vitamin K trials were similar. Fourth, some measurement bias and measurement error are inherent to complex decision-analytic models based on secondary data that often use simplifying assumptions to integrate parameter and structural uncertainty (286;287).

These limitations introduced an uncontrollable amount of error, difficult to disentangle and quantify, even with the use of advanced methodological approaches. Therefore, caution must be applied when interpreting the clinical aspect of our studies. Nonetheless, the methodological contributions are large: advanced and methodologically different methods are useful for investigating and corroborating uncertainty in the true effect of one treatment.
5.3 Suggestions for future research

Our research has identified important gaps in knowledge that need to be filled. In the following sections, we will describe suggestions for future investigations.

5.3.1 Vitamin K and fractures

Based on the univariate and bivariate meta-analyses, the K vitamins increase BMD at the lumbar spine and the femoral neck around 1%, an increase that can be also attained with vitamin D and calcium (206). The K vitamins tend to reduce the odds of fractures but the large uncertainties in the point estimates are persistent. Although the efficacies of the K vitamins may be smaller than the efficacy of pharmacological treatment, the K vitamins are shown to be safe as opposed to anti-resorptive therapy that can result in side effects including atypical femur fractures and osteonecrosis of jaw (288).

Therefore, we propose a future multicenter double-blind RCT to compare the efficacies of vitamin K2 (45 mg/day), vitamin K1 (5 mg/day) and both K vitamins against placebo on the incidence of vertebral and non-vertebral fractures over 3 years (i.e., a follow up in trials used to detect clinically important difference in incidence of fractures). The study population will include postmenopausal women with low BMD T-scores and low-to-moderate 10-year fracture risks ineligible for a pharmacological treatment but eligible for supplementation with vitamin D and calcium (13;14). Vitamin D and calcium will be given to all groups as per current clinical guidelines (13;14). Based on an expected incidence of fractures of 10% in the placebo group, we calculated that we would need 3213 women per group to give 80% power to detect a significant difference between vitamin K and placebo, corresponding to a 20% reduction of relative fracture risk (with a two-sided type I error of 5%). To detect a 25% or a 15% reduction in fracture risk, we would require approximately 2005 or 5860 women per group. Given that an anti-fracture effect of vitamin K may be explained through its effect on bone quality and not on BMD (17;18;20;71), the secondary outcome should include the mean changes of bone quality parameters (e.g., cortical thickness [mm], trabecular thickness [mm], trabecular number and trabecular spacing [mm⁻¹], trabecular bone volume/total volume, cortical and trabecular volumetric BMD [g/cm³]), as measured by high resolution peripheral
quantitative computed tomography. We also suggest conducting an economic patient-level study alongside this trial to calculate incremental net benefit (INB), the expected value of sample information (EVSI) and the expected net gain (ENG) (103;289-291). Based on the results of this trial and individual-level cost-effectiveness analysis, we will be able to determine if the adoption of vitamin K for the primary prevention of fractures in postmenopausal women represents good value for money.

5.3.2 Variability of outcome reporting: Osteoporosis research

Inconsistent reporting of BMD and fracture outcomes in the vitamin K trials was an important limitation of our evidence synthesis. As shown in our systematic review, the original studies presented changes in BMD as relative changes in BMD or BMD T-score (i.e., arithmetic mean percent change from baseline, mean percent difference and geometric mean percent change from baseline) and as absolute changes in areal BMD (i.e., mean change from baseline and MD [g/cm2]). Due to this variability in the reporting of effect measures, not all extracted data were pooled in the meta-analyses. Some variance data associated with changes in BMD were estimated from the original figures (published in the manuscripts). The point estimates and related variances and correlations were imputed in BRMA. It would be interesting to examine systematically the osteoporosis literature to determine the scope of variability in reporting of BMD and fracture outcomes, as those are the most often used in systematic reviews. Future investigations could also include surveys of experts, clinicians and scientists aimed to: 1) classify all bone outcomes from the most to the least important; 2) establish the least amount of outcome data that should be reported in the original studies; and, 3) recommend and standardize reporting of bone outcomes. This research can be a part of future methodological guidelines pertinent to designing, conducting, reporting and disseminating studies in osteoporosis research. The aims will be to facilitate valid and robust conclusions of systematic reviews and meta-analyses (considered the highest level of evidence) and to prevent investments in low-quality studies. These guidelines will improve accountability of the authors, journal editors and reviewers and will alleviate the risk of outcome reporting and dissemination bias.
5.3.3 Bayesian approach to explore uncertainty in the treatment effect: Comprehensive decision modeling and generalized evidence synthesis

We used a common modeling approach that is performed in two or more statistical packages referred to as “forward Monte Carlo simulation”, “two-step” or “classical” decision modeling (74;292-294). In this “two-stage” modeling, the distributions of input parameters such as treatment effects, probabilities and costs are summarized in the evidence synthesis (stage 1); in a separate analysis, these parameters are used to populate the cost-effectiveness models and perform PSA (stage 2). Consequently, the input parameters are treated as independent, though this is often not the case (74;292-294).

The Bayesian scientific community (74;292-294) has suggested another approach to decision modeling with a greater methodological potential. This approach is termed “Bayesian comprehensive decision modeling”; it integrates two processes – parameter estimation and uncertainty propagation – because Bayesian posteriors of the input parameters feed directly into the cost-effectiveness model. Therefore, within the same analysis, we can estimate the incremental benefits and incremental costs, incremental net benefit, probabilities of cost-effectiveness and the value of information (74;292-294).

This type of modeling requires Markov chain Monte Carlo simulations instead of Monte Carlo simulations because the evidence from the data is propagated “backward” to give the uncertainty on the parameters, which is then propagated “forward” through the cost-effectiveness model (74).

As compared to the classical “two-stage” modeling done in our studies, “Bayesian comprehensive decision modeling” has several advantages. First, in contrast to the “two-stage” approach, no distributional assumptions need to be specified on the input parameters since their posterior distributions were generated by updating the priors with observed data through Markov chain Monte Carlo simulations (74;292-294). Second, the Bayesian comprehensive decision modeling captures dependence between the parameters and simultaneously derives the joint posterior distribution of all unknown parameters (74;292-294). Third, it provides flexibility when modeling treatment effects. Within the comprehensive modeling approach, we can use Bayesian generalized evidence synthesis
to estimate the true treatment effects from different primary sources. We can account for bias associated with various study designs or use meta-regression to adjust for important covariates (74;80;226;285). BRMA or multivariate meta-analysis can be applied (127), and the methods of indirect comparisons can be used when head-to-head RCTs are not available (226;285;295). Lastly, through sensitivity analysis of the prior distributions specified on the mean treatment effect and the between-study heterogeneity parameters (139;141;142), we can thoroughly examine parameter uncertainty as well as decision uncertainty. With these methodological advantages,” Bayesian comprehensive decision modeling” appears as a method that merits further research.

5.3.4 Canadian Osteoporosis Microsimulation Policy Model

Almost one in two 50-year-old women can expect to sustain at least one major osteoporotic fracture in her lifetime (26). Patients with osteoporotic fractures have reduced quality of life and life expectancy and increased morbidity (5-9); they also incur large healthcare costs (10;12). If high-risk patients remain untreated, the personal and financial burdens pertinent to osteoporotic fractures will increase. Consequently, investigations of novel pharmacologic and non-pharmacologic therapies and other healthcare technologies are consistently undertaken, but due to financial or ethical constrains, these technologies are not evaluated over longer time-horizons, in all eligible populations, in various jurisdictions and against all eligible comparators (73;81;84;296). In these circumstances, we conduct decision-analytic studies and construct mathematical models to fill in the gaps in knowledge (73;75;78;297).

As indicated by Tosteson et al, BMD-based or fracture incidence-based mathematical models are used to reproduce the course of osteoporosis (298). To predict the occurrence of fractures, BMD-based models simulate changes in BMD over time alone or in addition to age and other risk factors, while fracture incidence-based models simulate published age-specific fracture incidence rates (298). Our assessment of the published models (up to 2012), shown in Table 5.3, suggests that fracture incidence-based models using probabilistic Markov transition-state microsimulation currently dominate the field. The BMD-based models take into account BMD status and use BMD testing to screen and diagnose osteoporosis. However, changes in BMD over time in patients diagnosed with
osteoporosis have a prognostic value (69). They are often used to evaluate the effect of
drug therapies over the clinical course of the disease. None of the published models
incorporated multiple BMD testing to examine the effects of pharmacologic treatments
over time in patients with osteoporosis and fractures (Table 5.3).

In comparison to other fracture incidence-based models, our model replicated the primary
prevention of fractures with vitamin D and calcium and the secondary prevention with
alendronate (196). It is a complex individual-level model that uses Monte Carlo
simulations and Markov cycle tree to accommodate 24 fracture health states consisting of
single and multiple fractures (same or different skeletal sites); it tracks the increased risks
of repeat fractures over time (for hip, vertebral and wrist fractures) and allows time-
dependency of several input parameters. In contrast to the other models, it uses the
shortest cycle length (1 month) to allow frequent occurrence of fractures and to prevent
overestimation or underestimation of fracture reduction with modeled therapies
(73;86;92). It estimates 10-year and lifetime probabilities of fractures (single and
multiple), life expectancy, quality-adjusted survival and other cost-effectiveness
outcomes, and it is calibrated against epidemiologic data. Although our model is
reasonably complex, it is still a simplified version of a real life clinical course of
osteoporosis. It also does not fulfill all requirements of a reference case analysis (e.g.,
not conducted from a societal perspective). It needs to be improved to be used for
decision-making on the broad allocation of health resources (81). Given the importance
of osteoporosis and the availability of Canadian population-based BMD, fracture and cost
data (10;299-301), we suggest that future research should focus on developing the
Canadian Osteoporosis Microsimulation Policy (COMP) model.
Table 5.3. Osteoporosis-related Markov state-transition models

<table>
<thead>
<tr>
<th>Description</th>
<th>Reference, year</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Canada</td>
<td>USA</td>
</tr>
<tr>
<td>Societal perspective</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Model</td>
<td>Microsimulation</td>
<td>Microsimulation</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Second-order (PSA), EVPI</td>
<td>Second-order (PSA)</td>
</tr>
<tr>
<td>Time horizon</td>
<td>Lifetime</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Cycle length</td>
<td>1 month</td>
<td>3 months</td>
</tr>
<tr>
<td>Simulations</td>
<td>1000 x 1000 trials</td>
<td>1,000,000 simulations</td>
</tr>
<tr>
<td>Natural history</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>BMD testing</td>
<td>No</td>
<td>Yes, screening test</td>
</tr>
<tr>
<td>Fracture states</td>
<td>Hip, vertebral, wrist: single and multiple</td>
<td>Hip, vertebral, wrist: single and multiple</td>
</tr>
<tr>
<td>Base-case age and sex</td>
<td>50 yrs, women</td>
<td>55 yrs, women</td>
</tr>
<tr>
<td>History of fracture</td>
<td>Using trackers Multiple fractures: increased risks of repeat fractures at the same or other sites, assuming an overall maximum risk adjustment</td>
<td>Modeled using trackers Multiple fractures: assumptions about modeling the risks of repeat fractures not stated</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Excess mortality after fracture</td>
<td>Hip (base-case), hip and vertebral (sensitivity)</td>
<td>Hip and vertebral</td>
</tr>
<tr>
<td>Treatment before fracture</td>
<td>Nothing, vitamins K2 or K1, vitamin D, calcium</td>
<td>Vitamin D, calcium</td>
</tr>
<tr>
<td>Treatment after fracture</td>
<td>Alendronate alone or alendronate + vitamins</td>
<td>Alendronate</td>
</tr>
<tr>
<td>Source: fracture data</td>
<td>Sweden</td>
<td>USA</td>
</tr>
<tr>
<td>Source: mortality data</td>
<td>Canada</td>
<td>USA</td>
</tr>
<tr>
<td>Source: costs</td>
<td>USA</td>
<td>USA</td>
</tr>
</tbody>
</table>
The COMP model can follow a blueprint of the American Coronary Heart Disease (CHD) policy model (311) that was developed to project the epidemiologic and cost data pertinent to CHD in the USA. It will be populated with Canadian demographic and epidemiologic data relevant to women and men age 50 years and over. It will be divided into two connected compartments, with the first replicating the detection of osteoporosis and the second simulating the primary, secondary or tertiary prevention of osteoporosis and osteoporotic fractures. The detection compartment will include BMD and FRAX testing as screening tools. The primary prevention model will simulate people at low risks of fractures and will evaluate the primary prevention strategies. The secondary prevention model will simulate patients at high risks of fractures or those with a first fracture (from the primary prevention model), eligible for and treated with various pharmacologic therapies. It will include hip, vertebral, wrist and other fracture states (single or repeat) and will replicate the clinical course of osteoporosis including routine serial BMD or bone turnover marker tests to evaluate the benefits and side-effects of bone drugs over time (69;312). It will also model diagnostic properties of radiographic assessments such as spinal X–rays radiography and DXA-based vertebral fracture assessment to identify the risk of asymptomatic vertebral fractures and simulate the course of osteoporosis in such populations (313). The tertiary prevention model will reproduce the course of osteoporosis after hip or other fractures and will evaluate procedures and processes such as hip replacement, vertebroplasty or kyphoplasty, outpatient care and rehabilitation (in nursing homes or elsewhere). The COMP model will integrate various methods of evidence synthesis and will be used to forecast osteoporosis-related epidemiologic and economic data. It will examine the long-term effects of bone drug therapies and will compare the effectiveness of novel technologies or different models of osteoporosis care. It will assist in making informed and transparent decisions regarding clinical practice, health policies and research funding in the area of osteoporosis.
6. Conclusions

To inform clinical practice and health policy, this thesis research evaluated the efficacy and the cost-effectiveness of the K vitamins for the prevention of osteoporotic fractures. It quantified uncertainties in the efficacies of the K vitamins using distinct methodological approaches: a cost-effectiveness analysis including microsimulation modeling and the EVPI, Bayesian univariate and bivariate random-effects meta-analyses. Since large uncertainties in the efficacies of vitamin K2 and vitamin K1 on fractures were consistently corroborated in all analyses, our study does not support implementation of the K vitamins for the primary prevention of fractures in postmenopausal women, until definitive evidence is obtained from future well-designed trials.

From a methodological perspective, our research illustrates that diverse methods should be combined to reflect and determine uncertainty in the true treatment effect. It shows that evidence synthesis should include multivariate or bivariate meta-analyses as treatment effects are often assessed on multiple and correlated outcomes. We show that in most cases, bivariate meta-analysis generates more precise estimates than univariate meta-analysis. Since it includes all available data, it likely alleviates outcome reporting bias, particularly, in meta-analyses of a small number of trials. We join the work of others (118;119;137), and support the value of using predictions of the true treatment effect in cost-effectiveness modeling, because it incorporates an additional and appropriate level of uncertainty. Since Bayesian comprehensive decision modeling integrates parameter estimation and uncertainty propagation within a single analysis and has the possibility of incorporating various analyses to estimate the effect of a treatment, future methodological investigations are needed to determine whether it could be more valid than the current “two-stage” modeling approach.

Finally, this thesis research resulted in a fracture incidence-based microsimulation state-transition model that can serve as a good basis for the development of a future more complex, clinically relevant osteoporosis model. This reference case model will assist clinicians, decision-makers and policy-makers to make informed choices concerning the allocation of healthcare resources and research funding in the area of osteoporosis.
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Appendices

7. Chapter 2: Appendices

7.1 Appendix 1: Parameter estimation

Transition probabilities

We used age and skeletal site-specific 10-year fracture probabilities of the Malmö Registry to estimate fracture probabilities in the model (157;160). The registry data are grouped by bone mineral density (BMD) T-scores and report 10-year probabilities of fractures for Swedish women age 50 years and older in 1993-1994 (157;160). Since our base-case was a 50-year-old woman with T-score above -2 and no prior fractures, we used the probabilities of hip, clinical vertebral and wrist fractures associated with the BMD T-score above -1 (as grouped in the Registry and available from the literature (160)) and the probabilities of morphometric vertebral fractures associated with BMD T-score of -2 (Table A2.1).

We transformed 10-year fracture probabilities into the monthly rates by assuming that the outcome times followed an exponential distribution(73;76). We calculated the monthly rate, $\mu$, as:

$$\mu = \frac{-\ln(1 - p)}{t}$$

where $p$ denotes the age-specific probability of a fracture and $t$ denotes the time period, in this case, 120. Probabilities were calculated for each fracture type and age stratum.

We modeled treatment effects by multiplying each rate by a relative hazard representing the effects of supplementation or alendronate. We assumed that odds ratios approximate relative hazards, which is a reasonable assumption for rare events(314).

We similarly adjusted rates to represent increased risks of subsequent fractures as a function of the location and number of prior fractures (161). We assumed that morphometric and clinical vertebral fractures increased the risk at the same rate. We assumed a maximum lifetime relative hazard for the fracture risk ($HR_{\text{max}}$) of 4 similar to the maximum risk of repeat fractures found in the literature (315). Thus, the relative hazard for fracture, $HR_f$ was calculated as:

$$HR_f = \min( \prod_{i=1}^{4} HR^{-n_i}, HR_{\text{max}} )$$
where \( i \) denotes the four type of fractures, \( HR_i \) denotes the fracture-specific relative hazard, \( n_i \) denotes the number of fractures, and \( HR_{\text{max}} \) denotes the maximum relative hazard.

The monthly probability of fracture, \( pf \), was calculated as:

\[
p_f = 1 - e^{\text{inc} \times HR_f}
\]

We used a similar approach to calculate mortality rates, incorporating an increased rate as function of the number of hip fractures. We assumed that the increased risk applied only in the 12 months, immediately following a fracture.

**Costs of vitamins K1 and K2**

Since the prices for vitamins K have not yet been established in the United States market, we estimated the costs of a 45mg daily dose of vitamin K2 from internet sources and incorporated the same shipping cost across the USA (Table A2.2). The daily price range was $1.7 to $9.9. Using a daily cost of $2.07 (as compared to the costs of vitamin D3 with calcium and vitamin K1), we calculated an annual cost of $865.20. We similarly calculated an annual cost of a 5 mg daily dose of vitamin K1 as used in the ECKO trial (60), assuming the same retail price as a 10 mg tablet (Table A2.3). Assuming a retail daily cost of vitamin K1 of $0.45, we calculated an annual cost of $199.80.

**Estimation of the efficacy of vitamin K1: The ECKO trial**

The ECKO trial (Evaluation of the Clinical use of vitamin K supplementation in postmenopausal women with Osteopenia) compared the effect of 5 mg/d vitamin K1 to placebo on bone density, vertebral and non-vertebral fractures in 440 postmenopausal Canadian women aged 50 and over with osteopenia (60). After 4 years of follow-up, the 217 women who received vitamin K1 had 7 incident fractures (0 hip, 1 clinical and 3 morphometric vertebral [grade II/III] and 3 wrist). The 223 women who received placebo had 19 incident fractures (1 hip, 0 clinical and 9 morphometric vertebral [grade II/III], and 9 wrist). The corresponding odds ratios were 0.34 (95%CI: 0.01-8.42) for hip fractures, 0.45 (95%CI: 0.14-1.47) for combined clinical and morphometric vertebral fractures and 0.33(95%CI: 0.09-1.25) for wrist fractures.
Input parameter distributions

We specified normal distributions of logarithm of odds ratios for the risk parameters and gamma distributions for the cost and utilities parameters (Table A2.4). We used the method of moments to estimate the means ($\mu$), variance ($\sigma^2$) (76;316) and to approximate the parameters of gamma distribution (Gamma ~ ($\alpha$, $\beta$)):

$$\alpha = \frac{\mu^2}{\sigma^2}$$

$$\beta = \frac{1}{\lambda} = \frac{1}{\mu / \sigma^2}.$$

7.2 Appendix 2: Additional results

Model calibration and predictions

Calibration results and predictions of first clinical fracture in women supplemented with nothing are presented in the main paper (Figures A2.1 and A2.2). In addition, our model suggested that 10-year probabilities of single fracture slightly varied between the age groups (19% at age 50 and 23% at age 80) while 10-year probabilities of multiple fractures steeply increased with age (from 4% at age 50 to 25% at age 80) (Figure A2.2).

Prevention of fractures with supplementation: 10-year fracture probabilities

Compared to vitamin D3 with calcium alone, supplementation with vitamins K2, D3 and calcium averted 5 to 8% of single and 2 to 14% of multiple fractures across different age groups (Figure A2.3). Corresponding fracture reductions with vitamin K1, vitamin D3 and calcium were 4 to 7% for single and 0 to 7% for multiple fractures (Figure A2.4).

Sensitivity analysis

We performed univariate (one-way) probabilistic sensitivity analyses to examine parameter uncertainty for the base case (vitamin K2) and vitamin K1 analyses. As described in details in the main paper, the incremental cost-effectiveness of vitamin K was dependant on the efficacy and the cost of vitamin K.
However, it was also dependent on the efficacy of vitamin D3 with calcium and alendronate under two unlikely assumptions. If the efficacy of vitamin D3 with calcium unexpectedly increased by more than half from 0.68 to 0.30 for hip fractures, 0.87 to 0.38 for vertebral fractures and 0.69 to 0.30 for wrist fractures, then the incremental cost-effectiveness of vitamin K2 would be associated with a ratio of $84,600/QALY. Similarly, the incremental cost-effectiveness of vitamin K1 was associated with a ratio of $118,953/QALY if the effect of alendronate on fractures was small or zero.

Results of sensitivity analyses related to our modeling assumptions are presented in Table A2.5. The cost-effectiveness of vitamin K was sensitive to changes in the time horizon. In vitamin K2 and vitamin K1 analyses, the incremental cost-effectiveness ratios exceeded $50,000/QALY if the time horizon decreased from lifetime to 10 years.

**Expected value of perfect information**

The expected value of perfect information (EVPI) determines the monetary value of removing all uncertainty related to the decision problem and is used to establish a need for future research (76;101;102). EVPI is the anticipated cost of obtaining the true value of all parameters that are currently uncertain (317). We calculated EVPI per patient, and multiplied it by the number of patients affected over the lifetime of the decision to compute the population EVPI (317). The calculations were performed using 1 million simulations (317). EVPI per patient was obtained as a difference between the expected value of a decision with perfect information about all uncertain parameters \( \theta \) and the optimal decision based on current information using the equation (76):

\[
EVPI = E_\theta \max_j NMB(j, \theta) - \max_j E_\theta NMB(j, \theta)
\]

where \( j \) is the optimal alternative, \( \theta \) is a value of the unknown parameters, and NMB is the net monetary benefit, calculated by subtracting the incremental cost from the product of the incremental benefit and the societal willingness to pay threshold for an additional unit of benefit.

We estimated the population EVPI using the US prevalence of 26 million for women 50 and older without osteoporosis (191) and the equation:

\[
Population EVPI = EVPI \times \frac{\sum I_t}{(1 + r)^t}
\]
where \( t \) denotes the time horizon (\( \leq 50 \) years), \( \text{It} \) is the incidence over time \( t \) and \( r \) is a discount rate(76).

We calculated the values of population EVPI for willingness to pay thresholds between $0 and $100,000/QALY for vitamin K2 and vitamin K1 (Figure A2.5). In both analyses, the population EVPI was higher than the anticipated costs of additional research, suggesting that future research should be performed before either vitamin K2 or vitamin K1 are adopted as concurrent treatment options for the primary prevention of fractures. Decision uncertainty for vitamin K2 as depicted by its population EVPI was the highest at the level of incremental cost-effectiveness ratio (Figure A2.5a) (76). The population EVPI for vitamin K1 increased steeply with increasing willingness-to-pay (Figure A2.5b), indicating substantial decision uncertainty. This may be explained by large uncertainty around the effect of vitamin K1 on all types of fractures, depicted by their wide probabilistic distributions (Table 2.1, main paper) (76).
Table A2.1. Input parameters: 10-year probabilities of fractures by skeletal sites

<table>
<thead>
<tr>
<th>PROBABILITIES OF FRACTURES</th>
<th>Base case (%)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Modeled as monthly changes within the model’s time horizon, with linear extrapolations (76))</td>
<td>(157;160)</td>
<td></td>
</tr>
<tr>
<td><strong>Hip fracture:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-year probabilities, by 5-year age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>14.6</td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td><strong>Morphometric vertebral fracture:</strong></td>
<td>(157;160)</td>
<td></td>
</tr>
<tr>
<td>10-year probabilities, by 5-year age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>15.1</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>17.2</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>18.7</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical vertebral fracture:</strong></td>
<td>(157;160)</td>
<td></td>
</tr>
<tr>
<td>10-year probabilities, by 5-year age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td><strong>Wrist fracture:</strong></td>
<td>(157;160)</td>
<td></td>
</tr>
<tr>
<td>10-year probabilities, by 5-year age groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-54</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>55-59</td>
<td>5.8</td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>7.9</td>
<td></td>
</tr>
<tr>
<td>75-79</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>80-84</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>85+</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Vitamin K2 (generic name)</td>
<td>Vitamin K2 (generic name)</td>
<td>Package: num of caps</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Glakay Menatetrenone</td>
<td>90</td>
<td>15</td>
</tr>
<tr>
<td>Glakay Menatetrenone</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Glakay Menatetrenone</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Glakay Menatetrenone</td>
<td>90</td>
<td>15</td>
</tr>
<tr>
<td>Glakay Menatetrenone</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Vitamin K2 Menatetrenone</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Vitamin K2 Menatetrenone</td>
<td>180</td>
<td>5</td>
</tr>
<tr>
<td>Vitamin K2 Menatetrenone</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Glakay Menatetrenone</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>

¹ The calculation of the cost of vitamin K2 was based on the studies using 45mg of vitamin K2 (calculated on April 30, 2010). For example, 3 caps of 15 mg per day is needed with a daily cost of $2.07 ($62.1/month). We assumed the same shipping cost across the US ($10/month for a bottle). This summed up to a total monthly cost for vitamin K2 (base case) of $72.1 ($865.2). Internet sources accessed on 27/06/2011.
Table A2.3. Vitamin K1 costs for the USA, internet sources

<table>
<thead>
<tr>
<th>Vitamin K1</th>
<th>Vitamin K1 (generic)</th>
<th>Package: num of caps</th>
<th>Dose /cap (mg)</th>
<th>Cost¹ ($US)</th>
<th>Shipping ($US)</th>
<th>Dose /day (mg)</th>
<th>Cost: per tablet ($US)</th>
<th>Cost: per day ($US)</th>
<th>Cost: 30-day ($US)</th>
<th>Internet source</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSI Vitamin K-1</td>
<td>phytonadione</td>
<td>90</td>
<td>10</td>
<td>14.99</td>
<td>10.00</td>
<td>5</td>
<td>0.17</td>
<td>0.16</td>
<td>4.99</td>
<td><a href="http://www.vitacost.com/NSI-Vitamin-K-1?src=NTDC-835003001361#IngredientFacts">http://www.vitacost.com/NSI-Vitamin-K-1?src=NTDC-835003001361#IngredientFacts</a></td>
</tr>
<tr>
<td>NSI Vitamin K-1</td>
<td>phytonadione</td>
<td>90</td>
<td>10</td>
<td>39.95</td>
<td>10.00</td>
<td>5</td>
<td>0.45</td>
<td>0.45</td>
<td>13.32</td>
<td>retail price, NSI</td>
</tr>
</tbody>
</table>

¹ The calculation of the cost of vitamin K1 was based on the dose of 5 mg used in the ECKO trial [8]. We assumed the cost of a 10mg package. We used a higher retail price of $39.95 that included 90 caps (a 30-day supply was assumed to be 1/3 of the package). We assumed that one bottle was shipped every 3 months with a domestic shipping cost same across the USA ($3.33/month). This summed up to a total monthly cost of $16.65 ($199.8/ year). Internet sources accessed on 27/06/2011.
### Table A2.4a. Parameter distributions: Risks

<table>
<thead>
<tr>
<th>RISKS</th>
<th>OR (95% CI)</th>
<th>Normal distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Next fracture following</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>2.4 (95% CI: 1.9-3.2)</td>
<td>N (0.87, 0.017)</td>
<td>(161)</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>2.0 (95% CI: 1.7-2.4)</td>
<td>N (0.64, 0.006)</td>
<td>(161)</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>1.9 (95% CI: 1.7-2.3)</td>
<td>N (0.69, 0.008)</td>
<td>(161)</td>
</tr>
<tr>
<td>Death, 1st year following a hip fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fracture risk with alendronate (70 mg/week)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.62 (95% CI: 0.40-0.98)</td>
<td>N (-0.48, 0.053)</td>
<td>(175)</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.56 (95% CI: 0.46-0.68)</td>
<td>N (-0.58, 0.010)</td>
<td>(175)</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.64 (95% CI: 0.30-1.35)</td>
<td>N (-0.45, 0.144)</td>
<td>(175)</td>
</tr>
<tr>
<td>Fracture risk with vitamin D3 plus calcium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.68 (95% CI: 0.50-0.92)</td>
<td>N (-0.38, 0.026)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.87 (95% CI: 0.65-1.14)</td>
<td>N (-0.14, 0.019)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.69 (95% CI: 0.18-2.54)</td>
<td>N (-0.37, 0.449)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Fracture risk with vitamin K2 (45 mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.30 (95% CI: 0.05-1.74)</td>
<td>N (-1.20, 0.828)</td>
<td>(56)§</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.40 (95% CI: 0.25-0.65)</td>
<td>N (-0.92, 0.058)</td>
<td>(56)</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.54 (95% CI: 0.20-0.85)</td>
<td>N (-0.62, 0.137)</td>
<td>(168)</td>
</tr>
<tr>
<td>Fracture risk with vitamin K1 (5 mg/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.34 (95% CI: 0.01-8.42)</td>
<td>N (-1.08, 2.958)</td>
<td>ECKO, (60)</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.45 (95% CI: 0.14-1.47)</td>
<td>N (-0.79, 0.348)</td>
<td>ECKO</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.33 (95% CI: 0.09-1.25)</td>
<td>N (-1.11, 0.449)</td>
<td>ECKO</td>
</tr>
</tbody>
</table>

OR= odds ratio; 95% CI= 95% confidence interval; s = standard deviation; § Subgroup analysis excluding the Sato studies (172-174)

### Table A2.4b. Parameter distributions: Utilities and costs

<table>
<thead>
<tr>
<th>UTILITIES and COSTS</th>
<th>µ ± s*</th>
<th>s²</th>
<th>α</th>
<th>Gamma distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTILITIES</td>
<td></td>
<td></td>
<td></td>
<td>Gamma ~ (α, β)</td>
<td></td>
</tr>
<tr>
<td>Hip fracture, first year</td>
<td>0.89 ± 0.043</td>
<td>0.00185</td>
<td>424.8</td>
<td>α= 424.8 ; β=0.00017</td>
<td>(178)</td>
</tr>
<tr>
<td>Hip fracture, subsequent years</td>
<td>0.925 ± 0.048</td>
<td>0.0023</td>
<td>371.5</td>
<td>α= 371.5 ; β=0.000207</td>
<td>(175)</td>
</tr>
<tr>
<td>Clinical vertebral, first year</td>
<td>0.90 ± 0.031</td>
<td>0.00096</td>
<td>0.0014</td>
<td>α= 0.0014 ; β=53.3</td>
<td>(178)</td>
</tr>
<tr>
<td>Clinical vertebral, subsequent years</td>
<td>0.93 ± 0.008</td>
<td>0.00006</td>
<td>0.0015</td>
<td>α= 0.0015 ; β=51.61</td>
<td>(175)</td>
</tr>
<tr>
<td>Wrist fracture</td>
<td>0.98 ± 0.005</td>
<td>0.00002</td>
<td>0.0017</td>
<td>α= 0.0017 ; β=48.96</td>
<td>(175)</td>
</tr>
<tr>
<td>No fracture</td>
<td>0.985 ± 0.01</td>
<td>0.0001</td>
<td>0.0017</td>
<td>α= 0.0017 ; β=48.72</td>
<td>(181)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COSTS (US)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture, first year</td>
<td>51,139.2 ± 12785</td>
<td>163.45*10⁶</td>
<td>16.00</td>
<td>α= 16.00 ; β=266.35</td>
<td>(11)</td>
</tr>
<tr>
<td>Hip fracture, 2-5 years</td>
<td>3,639.9 ± 910</td>
<td>0.83*10⁶</td>
<td>15.9981</td>
<td>α= 15.9981 ; β=18.96</td>
<td>(11)</td>
</tr>
<tr>
<td>Clinical vertebral, first year</td>
<td>1,659.4 ± 415</td>
<td>0.17*10⁶</td>
<td>15.9958</td>
<td>α= 15.9958 ; β=8.64</td>
<td>(11)</td>
</tr>
<tr>
<td>Clinical vertebral, 2-5 years</td>
<td>371.9 ± 93</td>
<td>8643.4</td>
<td>16.00</td>
<td>α= 16.00 ; β=1.94</td>
<td>(11)</td>
</tr>
<tr>
<td>Wrist fracture, first year</td>
<td>1030.3 ± 258</td>
<td>0.067*10⁶</td>
<td>15.9932</td>
<td>α= 15.9932 ; β=5.37</td>
<td>(11)</td>
</tr>
<tr>
<td>Alendronate, 70 mg/wk (generic)</td>
<td>131.0</td>
<td>NA</td>
<td>NA</td>
<td>Fixed</td>
<td>(158)</td>
</tr>
<tr>
<td>Vitamin K2, 45 mg/day</td>
<td>865.2 ± 216</td>
<td>0.047*10⁶</td>
<td>16.00</td>
<td>α= 16.00 ; β=4.51</td>
<td>(185)</td>
</tr>
<tr>
<td>Vitamin K1, 5 mg/day</td>
<td>199.8 ± 50</td>
<td>2495</td>
<td>15.9987</td>
<td>α= 15.9987 ; β=0.16</td>
<td>(183)</td>
</tr>
<tr>
<td>Vitamin D3 with calcium, 800 IU + 1200 mg/day</td>
<td>89.9 ± 229</td>
<td>505.8</td>
<td>15.9957</td>
<td>α= 15.9957 ; β=0.47</td>
<td>(158)</td>
</tr>
</tbody>
</table>

µ= mean; s = standard deviation; s²= variance; s for costs is assumed 25% of the mean cost (µ); NA= not applicable.
### Table A2.5. Sensitivity analyses: Vitamin K2 and vitamin K1

<table>
<thead>
<tr>
<th>Assumptions¹</th>
<th>Changes in assumptions</th>
<th>Vitamin K2 § ICER ($/QALY)</th>
<th>Vitamin K1 † ICER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case'</strong></td>
<td>NA</td>
<td>18,440</td>
<td>8,631</td>
</tr>
<tr>
<td><strong>Duration of drug benefit</strong></td>
<td>Length of drug benefit changed from 10 years to lifetime</td>
<td>12,551</td>
<td>12,434</td>
</tr>
<tr>
<td><strong>Compliance to all treatments</strong></td>
<td>50%</td>
<td>10,738</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80%</td>
<td>7,103</td>
<td></td>
</tr>
<tr>
<td><strong>Utility changes over time</strong></td>
<td>Change of all fracture utilities in the first year only</td>
<td>19,850</td>
<td>8,162</td>
</tr>
<tr>
<td></td>
<td>Change of all fracture utilities in the first and subsequent years for hip and vertebral fractures, with utilities exponentiated to the number of hip and vertebral fractures</td>
<td>16,527</td>
<td>7,914</td>
</tr>
<tr>
<td><strong>Lifetime maximum number of fractures</strong></td>
<td>Low: 1 hip, 2 clinical vertebral, 4 morphometric vertebral, 1 wrist fractures</td>
<td>17,573</td>
<td>13,574</td>
</tr>
<tr>
<td></td>
<td>High: 6 hip, 12 clinical vertebral, 18 morphometric vertebral, 8 wrist fractures</td>
<td>13,202</td>
<td>63,609</td>
</tr>
<tr>
<td><strong>Excess mortality due to vertebral fractures</strong></td>
<td>1 year</td>
<td>16,474</td>
<td>29,465</td>
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<tr>
<td></td>
<td>5 years</td>
<td>20,223</td>
<td>3,932</td>
</tr>
<tr>
<td><strong>Base case age</strong></td>
<td>Age 60</td>
<td>5,926</td>
<td>35,360</td>
</tr>
<tr>
<td></td>
<td>Age 70</td>
<td>*</td>
<td>19,298</td>
</tr>
<tr>
<td></td>
<td>Age 80</td>
<td>*</td>
<td>535</td>
</tr>
<tr>
<td><strong>Time horizon (base case age = 50)</strong></td>
<td>10 years</td>
<td>1,598,830 ‡</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>20 years</td>
<td>149,462 †</td>
<td>162,557 †</td>
</tr>
<tr>
<td></td>
<td>30 years</td>
<td>39,089</td>
<td>49,255</td>
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<td></td>
<td>40 years</td>
<td>19,491</td>
<td>1,839,582 ‡</td>
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<tr>
<td><strong>10-year time horizon with and the age of base case changing from 50 to 60, 70 or 80 years</strong></td>
<td>Base case = 60</td>
<td>224,356 ‡</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Base case = 70</td>
<td>56,521 †</td>
<td>6,158,962 ‡</td>
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<tr>
<td></td>
<td>Base case = 80</td>
<td>*</td>
<td>142,833 ‡</td>
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</table>

¹ These were probabilistic sensitivity analyses on a sample of 10,000 iterations. Base case assumptions: 1) duration of drug benefit with alendronate of 10 years; 2) compliance to all treatments of 100%; 3) change in hip and vertebral fracture utility weights in the first and subsequent years; 4) lifetime maximum numbers of fractures: hip =2, vertebrae= 4 clinical and 8 morphometric and wrist =2; 5) no excess mortality risk due to clinical vertebral fractures; 6) base case age of 50; 7) time horizon of 50 years. § Vitamin K2 analysis: compares vitamin K2 with vitamin D3 and calcium to vitamin D3 with calcium alone; † Vitamin K1 is a corresponding analysis replacing vitamin K2 with vitamin K1; ICER = incremental cost-effectiveness ratio; ‡ Vitamin K2 or K1 was associated with incremental effectiveness (ΔE >0) but also high incremental costs (ΔC >0), yielding the ICERs > $50,000 / QALY. * Negative ICERs (meaningless).
7.4 Appendix 4: Figures

Figure A2.1a: Observed and modeled probabilities – hip fractures

Figure A2.1b: Observed and modeled probabilities – morphometric vertebral fractures
Figure A2.1c: Observed and modeled probabilities – clinical vertebral fractures

Figure A2.1d: Observed and modeled probabilities – wrist fractures
Figure A2.2. Model predictions: Single and multiple fractures, lifetime and 10-year probabilities

Figure A2.3. Vitamin K2: 10-year fracture probabilities
Figure A2.4. Vitamin K1: Age-specific 10-year fracture probabilities
Figure A2.5. EVPI by a willingness-to-pay threshold: Vitamin K2 (Figure A5a) and vitamin K1 (Figure A5b). Probabilistic sensitivity analyses included 1 million simulations to calculate population EVPI ($US, billion) assuming the prevalence of osteopenia in US women age 50 of 26 million.
8. Chapter 3: Appendices

8.1 Appendix 1: Tables
<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparison</th>
<th>Sample (vitamin K /control)</th>
<th>Lumbar Spine For each group</th>
<th>Femoral Neck For each group</th>
<th>Total Hip For each group</th>
<th>Radius (DR‡, UDR‡‡) For each group</th>
<th>Fractures (vitamin K /control)</th>
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<tbody>
<tr>
<td></td>
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<td>mean % change (SD)</td>
<td>Mean change-g/cm² (SD)</td>
<td>Mean % change in T-score (SD)</td>
<td>Mean change-g/cm² (SD)</td>
<td>Absolute: % change (SD)</td>
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<td></td>
<td></td>
<td>Mean % change in T-score</td>
<td>geometric % mean change</td>
<td>Mean % change in T-score</td>
<td>geometric % mean change</td>
<td>Fractures: % change (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(SD)</td>
<td>(SD)</td>
<td>(SD)</td>
<td>(SD)</td>
<td>(SD)</td>
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<td></td>
<td></td>
<td>geometric % MD (SD)</td>
<td>geometric % MD (SD)</td>
<td>geometric % MD (SD)</td>
<td>geometric % MD (SD)</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td>Hip</td>
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<td>Iwamoto, 1999¹</td>
<td>K2 vs. D</td>
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<td>%Mean change: 0.23(1.9) / -2.87 (2.2)</td>
<td>NR</td>
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<td>NR</td>
<td>NR</td>
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<td>K2 vs. combined controls ²</td>
<td>51/58</td>
<td>%Mean change: 0.23(1.9)/ 0.52(5.0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>K2 vs. D</td>
<td>22/29</td>
<td>%Mean change: 0.90 (2.1)/ 0.38 (3.4)</td>
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<td>K2 and K2+D vs. combined controls ²</td>
<td>108/119</td>
<td>%Mean change: 1.08(1.9)/ 0.23 (2.6)</td>
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<td>Shiraki, 2000</td>
<td>K2 vs. calcium</td>
<td>91/99</td>
<td>%Mean change: -0.50(10.9)/ -3.2 (9.4)</td>
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<td>NR</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Ushiroyama, 2002 ¹</td>
<td>K2 alone vs. no tx</td>
<td>30/33</td>
<td>%Mean change: 0.14(5.4)/ -3.47 (2.8)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Ushiroyama, 2002 ²</td>
<td>K2 and K2+D vs. combined controls ²</td>
<td>152/161</td>
<td>%Mean change: 2.09(6.9)/ -0.42(6.0)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Ishida, 2004</td>
<td>K2 alone vs. no tx</td>
<td>66/66</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yasui, 2006</td>
<td>K2 + D3 vs. K2</td>
<td>17/17</td>
<td>Absolute: 0.685 (0.04) / 0.707 (0.06)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Purwosunu, 2006</td>
<td>K2 vs. placebo</td>
<td>33/30</td>
<td>%Mean change: 1.74(2.1) / 0.18(1.3)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Knappen, 2007</td>
<td>K2 vs. placebo</td>
<td>161/164</td>
<td>%Mean change: 0.22(4.1)/ 0.5 (4.4)</td>
<td>%Mean change: -2.50(5.26)/ 2.57 (4.42)</td>
<td>%Mean change: -2.0 (3.6)/ 1.50(4.4)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hirao, 2008</td>
<td>K2 vs. alendronate</td>
<td>21/23</td>
<td>%Mean change in T-score: 6.00(8.0)/4.00(9.6)</td>
<td>%Mean change: -2.5(13.1) / 0.012 (0.04)</td>
<td>%Mean change: -0.04(0.02)/ -0.005(0.02)</td>
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<td>NR</td>
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<tr>
<td>Inoue, 2009 ³</td>
<td>K2 vs. calcium</td>
<td>1372/1381</td>
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<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Inoue, 2009 ³</td>
<td>K2 vs. calcium</td>
<td>627/635</td>
<td>%Mean change: -0.45(3.4)/ -0.50(3.6); absolute: -0.006 (0.04) / -0.012 (0.04)</td>
<td>%Mean change: -0.38 (2.54)/ -0.54 (2.41); Absolute: -0.004 (0.02)/ -0.005 (0.02)</td>
<td>%Mean change: -0.41(2.2)/ -0.35(2.0); -0.004 (0.02)/ -0.003 (0.02)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Emaus, 2010</td>
<td>K2 vs. placebo</td>
<td>167/167</td>
<td>%Mean change: -0.32(4.3)/ 0.55(3.1); Geometric %MD: -6.0(3.33)</td>
<td>%Mean change: -0.18(2.6)/ 0.2(2.7); Geometric %MD: -2.0(5.5)</td>
<td>%Mean change: -0.19(2.6)/ 0.2(2.7); Geometric %MD: -2.0(5.5)</td>
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<td>NR</td>
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<tr>
<td>Binkley, 2009</td>
<td>K2 vs. placebo</td>
<td>126/129</td>
<td>%Mean change: -0.32(4.3)/ 0.55(3.1); Geometric %MD: -6.0(3.33)</td>
<td>%Mean change: -0.18(2.6)/ 0.2(2.7); Geometric %MD: -2.0(5.5)</td>
<td>%Mean change: -0.19(2.6)/ 0.2(2.7); Geometric %MD: -2.0(5.5)</td>
<td>NR</td>
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<tr>
<td>Trial</td>
<td>Sample (vitamin K / control)</td>
<td>Lumbar Spine</td>
<td>Femoral Neck</td>
<td>Total Hip</td>
<td>Radius (DR‡, UDR‡‡)</td>
<td>Fractures (vitamin K / control)</td>
<td></td>
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<tr>
<td>---------------</td>
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<tr>
<td></td>
<td></td>
<td>For each group</td>
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<td>For each group</td>
<td>For each group</td>
<td>All</td>
<td>Non-vertebral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mean % change (SD)</td>
<td>mean % change (SD)</td>
<td>mean % change (SD)</td>
<td>mean % change (SD)</td>
<td>Non-vertebral</td>
<td>Vertebral</td>
</tr>
<tr>
<td>Schafsma, 2002</td>
<td>K1 vs. placebo</td>
<td>22/27</td>
<td>% Mean change: 0.52(2.1)/0.13(2.3)</td>
<td>% Mean change: 1.48(4.7)/0.6(3.5)</td>
<td>% Mean change: 0.23(3.5)/0.14(4.3)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Braam, 2003¹</td>
<td>K1 vs. placebo</td>
<td>56/60</td>
<td>% MD: 0.5 (0.7)</td>
<td>% Mean change: -3.4 (4.5)/ -4.9 (3.5)</td>
<td>% MD: 1.7 (0.8)</td>
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<td>NR</td>
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<tr>
<td>Braam, 2003²</td>
<td>K1 vs. combined controls²</td>
<td>112/106</td>
<td>% MD: 0.62 (0.7)</td>
<td>% Mean change: -3.4 (4.5)/ 5.12 (3.3)</td>
<td>% MD: 1.51 (0.8)</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Bolton-Smith, 2007¹</td>
<td>K1 vs. placebo</td>
<td>54/56</td>
<td>NR</td>
<td>Absolute: -0.0042 (0.04)/0.007 (0.04)</td>
<td>Absolute: -0.0012 (0.04)/0.003 (0.04)</td>
<td>NR</td>
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<tr>
<td>Bolton-Smith, 2007²</td>
<td>K1 &amp; K1+D+calcium vs. combined controls²</td>
<td>255/266</td>
<td>NR</td>
<td>Absolute: 0.0019 (0.02)/0.036 (0.01)</td>
<td>NR</td>
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<tr>
<td>Booth, 2008³</td>
<td>K1 vs. placebo</td>
<td>134/133</td>
<td>% Mean change: 0.90 (4.87)/1.90 (4.90)</td>
<td>Absolute: 0.044 (0.05)/0.043 (0.05)</td>
<td>Absolute: -0.046 (3.2)/0.27 (4.2)</td>
<td>Absolute: -0.009 (0.04)/0.008 (0.04)</td>
<td>NR</td>
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<tr>
<td>Cheung, 2008</td>
<td>K1 vs. placebo</td>
<td>217/223</td>
<td>% Mean change: -1.29 (3.5)/1.22 (2.9)</td>
<td>% MD: -0.06 (0.3)</td>
<td>% Mean change: -1.47 (3.8)/1.84 (3.5)</td>
<td>% Mean change: -0.00 (2.6)/0.07 (2.6)</td>
<td>% MD: -0.19 (0.5)</td>
</tr>
<tr>
<td>Binkley, 2009</td>
<td>K1 vs. placebo</td>
<td>126/129</td>
<td>% MD: 0.5 (0.3)</td>
<td>% Mean change: -0.32 (4.3)/0.55 (3.1)</td>
<td>Standardized % MD: -0.06 (0.3)</td>
<td>Mean change (g/cm²) [95%CI]: K1: 0.016 (-0.005; 0.036), K2: 0.006 (-0.018; 0.026), CaD: -0.008 (-0.011; 0.05), Control: -0.032 (-0.046; -0.01)</td>
<td>NR</td>
</tr>
<tr>
<td>Mochanis, 2011</td>
<td>K1 + vitamin D+ calcium vs. K2 + vitamin D + calcium vs. Vitamin D + calcium vs. No treatment</td>
<td>26/24/26/39</td>
<td>% Mean change: -1.29 (3.5)/1.22 (2.9)</td>
<td>% MD: 0.5 (0.3)</td>
<td>% Mean change: -0.32 (4.3)/0.55 (3.1)</td>
<td>Mean change (g/cm²) [95%CI]: K1: 0.016 (-0.005; 0.036), K2: 0.006 (-0.018; 0.026), CaD: -0.008 (-0.011; 0.05), Control: -0.032 (-0.046; -0.01)</td>
<td>NR</td>
</tr>
</tbody>
</table>

⁴ NR denotes lack of any reported data for the listed outcomes; ⁵ Assumed the same values for both sexes; MD denotes a mean difference; ¹ denotes data for reference analysis where vitamin K is compared to one control group; ² denotes data for sensitivity analyses where vitamin K is compared to multiple control groups (data combined); ³ denotes a trial including patients without fractures and ⁴ denotes a trial including patients with fractures.
Table A3.2. Risk of bias of the included trials

<table>
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<th>Author</th>
<th>Within-study bias</th>
<th>Allocation sequence generated</th>
<th>Allocation concealed</th>
<th>Blinding: primary outcome</th>
<th>Blinding: secondary outcome</th>
<th>Incomplete data adequately addressed (ITT): primary outcome</th>
<th>Incomplete data adequately addressed (ITT): secondary outcome</th>
<th>Selective outcome report</th>
<th>Total LFU</th>
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<td>Bolton-Smith, 07</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>0.14</td>
</tr>
<tr>
<td>Braam, 2003</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>0.14</td>
</tr>
<tr>
<td>Schaafsma, 02</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>0.16</td>
</tr>
<tr>
<td>Cheung, 2008</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Table A3.3. Additional results of the Bayesian and classical meta-analyses including data from multiple control and vitamin K2 arms (sensitivity analysis): the mean percent change in BMD at the lumbar spine

<table>
<thead>
<tr>
<th>Postiors</th>
<th>Sensitivity Analysis: Bayesian</th>
<th>Reference Analysis: Bayesian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (% change in BMD)</td>
<td>Mean (% change in BMD)</td>
</tr>
<tr>
<td></td>
<td>(95% Credible Interval)</td>
<td>(95% Credible Interval)</td>
</tr>
<tr>
<td>Mean difference (MD): current</td>
<td>0.75 (-0.33,1.89)</td>
<td>1.24 (-0.01,2.53)</td>
</tr>
<tr>
<td>studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD: future study</td>
<td>0.75 (-2.33,3.88)</td>
<td>1.24 (-2.27,4.81)</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>1.36 (0.65,2.15)</td>
<td>1.61 (0.89,2.20)</td>
</tr>
<tr>
<td>Variance</td>
<td>2.03 (0.42,4.63)</td>
<td>2.71 (0.80,4.83)</td>
</tr>
<tr>
<td>Probability of benefit ≥ 1%</td>
<td>69%</td>
<td>88%</td>
</tr>
<tr>
<td>increase:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current studies</td>
<td>57%</td>
<td>67%</td>
</tr>
<tr>
<td>Future study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of any increase in</td>
<td>92%</td>
<td>97%</td>
</tr>
<tr>
<td>BMD:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current studies</td>
<td>71%</td>
<td>77%</td>
</tr>
<tr>
<td>Future study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                                 | Sensitivity Analysis: Classical | Reference Analysis: Classical |
|                                 | Pooled Estimate (95% Credible Interval) | Pooled Estimate (95% Credible Interval) |
| MD                              | 0.71 (-0.06,1.49)               | 1.20 (0.15,2.25)               |
| Variance                        | 0.9                             | 1.76                           |
8.2 Appendix 2: Figures

Figure A3.1. Search strategies

**Ovid MEDLINE(R): 1948 to Dec 2012**

001 exp Vitamin K/
002 vitamin k*.mp.
003 menaquinone*.mp.
004 mk-4.mp.
005 mk-7.mp.
006 phylloquinone*.mp.
007 konakion*.mp.
008 phytonadione*.mp.
009 menadione*.mp.
010 aquamephyton*.mp.
011 menadiol*.mp.
012 mephyton*.mp.
013 phytomenadione*.mp.
014 menatetrenone*.mp.
015 exp vitamin K deficiency/
016 or/1-15
017 exp "Bone and Bones"/
018 exp Fractures, Bone/
019 exp Bone Diseases/
020 exp Musculoskeletal Physiological Phenomena/
021 bone*.mp.
022 osteo*.mp.
023 or/17-22
024 23 and 16
025 exp dietary supplements/
026 exp food, fortified/
027 25 or 26
028 27 and 16
029 28 or 24

**EMBASE Classic+EMBASE: 1947 to Dec 2012**

001 exp Vitamin K/
002 vitamin k*.mp.
003 menaquinone*.mp.
004 mk-4.mp.
005 MK-4*.mp.
006 MK-7*.mp.
007 phylloquinone*.mp.
008 konakion*.mp.
009 phytonadione*.mp.
010 menadione*.mp.
011 aquamephyton*.mp.
012 menadiol*.mp.
013 mephyton*.mp.
014 phytomenadione*.mp.
015 menatetrenone*.mp.
016 farnoquinone*.mp.
017 exp vitamin K deficiency/
018 or/1-17
019 exp bone/
020 exp bone fragility/ or exp bone metabolism/ or exp iliac bon
e/ or exp bone age/ or exp long bone/ or exp bone remodeling
/ or exp "bone characteristics and functions"/ or exp bone dysplasia/ or exp bone turnover/ or exp bone density/ or exp bone structure/ or exp cortical bone/ or exp cancellous bone
/ or exp bone densitometry/ or exp metatarsal bone/ or exp pubic bone/ or exp involutional bone loss/ or exp metacarpal bone/ or exp endocrine bone disease/ or exp metabolic bone disease/ or exp bone deformation/ or exp bone regeneration/ or exp bone strength/ or exp coccygeal bone/ or exp alkaline phosphatase bone isoenzyme/ or exp bone demineralization/ or exp carpal bone/ or exp bone mineral/ or exp bone disease/ or exp metacarpal bone fracture/ or exp bone/ or exp bone tissue/ or exp trabecular bone/ or exp bone mass/ or exp bone mineralization/
021 exp fracture/
022 exp bone disease/
023 corticosteroid induced osteoporosis/ or idiopathic osteoporosis/ or postmenopause osteoporosis/ or postmenopause osteoporosis/ or posttraumatic osteoporosis/ or primary osteoporosis/ or secondary osteoporosis/ or senile osteoporosis/
024 22 or 21 or 23 or 20
025 bone*.mp.
026 osteo*.mp.
027 25 or 24 or 26
028 exp supplementation/ or exp diet supplementation/ or exp vitamin supplementation/
029 28 and 18
030 18 or 29
031 27 and 30

CINAHL: 1981- Dec 2012
S68 S64 or S67
S67 S52 and S66
S66 (MH "Fractures+)
S65 fractures
S64 S56 or S63
S63 S52 and S62
S62 S57 or S58 or S59 or S60 or S61
S61 TX osteo*
S60 TX bone*
S59 (MH "Musculoskeletal System Physiology+
S58 (MH "Bone Diseases+
S57 (MH "Bone and Bones+
S56 S52 and S55
S55 S53 or S54
S54 (MH "Food, Fortified")
S53 (MH "Dietary Supplements+
S52 S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51
S51 TX menatetrenone*
S50 TX phytomenadione*
S49 TX mephyton*
S48 aqua mephyton*
S47 mephyton*
S46 menadiol*
S45 aquamephyton*
S44 menadione*
S43 phytonadione*

001 vitamin k*.mp.
002 menaquionone*.mp.
003 mk-4.mp.
004 MK-4*.mp.
005 MK-7*.mp.
006 phyloquinone*.mp.
007 konakion*.mp.
008 phytonadione*.mp.
009 menadione*.mp.
010 aquamephyton*.mp.
011 menadiol*.mp.
012 mephyton*.mp.
013 phytomenadione*.mp.
menatetrenone*.mp.
farnoquinone*.mp.
corticosteroid induced osteoporosis/ or idiopathic osteoporosis/ or postmenopause osteoporosis/ or posttraumatic osteoporosis/ or primary osteoporosis/ or secondary osteoporosis/ or senile osteoporosis/

bone*.mp.
oste*.mp.
bone disease
or/1-15
or/16-19
20 and 21

AMED (Allied and Complementary Medicine): 1985 to Dec 2012
exp Vitamin K/
vitamin k*.mp.
konakion*.mp.
phytonadione*.mp.
exp bone fragility/ or exp bone metabolism/ or exp iliac bone/ or exp bone age/ or exp long bone/ or exp bone remodeling/ or exp "bone characteristics and functions"/ or exp bone dysplasia/ or exp bone turnover/ or exp bone density/ or exp bone structure/ or exp cortical bone/ or exp cancellous bone/ or exp bone densitometry/ or exp metatarsal bone/ or exp pubic bone/ or exp involutional bone loss/ or exp metacarpal bone/ or exp endocrine bone disease/ or exp metabolic bone disease/ or exp bone deformation/ or exp bone regeneration/ or exp bone strength/ or exp coccygeal bone/ or exp alkaline phosphatase bone isoenzyme/ or exp bone demineralization/ or exp carpal bone/ or exp bone mineral/ or exp bone disease/ or exp metacarpal bone fracture/ or exp bone/ or exp bone tissue/ or exp trabecular bone/ or exp bone mass/ or exp bone mineralization/
exp bone disease/
corticosteroid induced osteoporosis/ or idiopathic osteoporosis/ or postmenopause osteoporosis/ or posttraumatic osteoporosis/ or primary osteoporosis/ or secondary osteoporosis/ or senile osteoporosis/
bone*.mp.
oste*.mp.
vitamin k/ or vitamin k 2/ or vitamin k 3/
4 or 1 or 3 or 10 or 2
8 or 6 or 7 or 9 or 5
11 and 12
Figure A3.2a. Examples of calculations of the mean treatment effects and standard deviations for multi-arm trials. The weighted mean approach (Formula 1) and the correlation approach (Formula 2)

<table>
<thead>
<tr>
<th>Multiarm Study</th>
<th>Treatment group (% change)</th>
<th>SD - sample</th>
<th>Sample: treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwamoto_2000 K2+D vs. Calcium</td>
<td>1.35 1.72</td>
<td>21</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD - control</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sample: control</td>
</tr>
<tr>
<td></td>
<td>-0.79 1.12</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Iwamoto_2000 K2+D vs.Dalone</td>
<td>1.35 1.72</td>
<td>21</td>
<td>0.38 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Iwamoto_2000 Mean (averages)</td>
<td>1.35 1.72</td>
<td>21</td>
<td>-0.205 2.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24.5</td>
</tr>
<tr>
<td>Iwamoto_2000 K2 vs.Dalone</td>
<td>0.9 1.88</td>
<td>22</td>
<td>0.38 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Iwamoto_2000 K2 vs.K+D</td>
<td>0.9 1.88</td>
<td>22</td>
<td>1.35 1.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Iwamoto_2000 K2 vs.Calcium</td>
<td>0.9 1.88</td>
<td>22</td>
<td>-0.79 1.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Iwamoto_2000 Mean (averages)</td>
<td>0.9 1.88</td>
<td>22</td>
<td>0.313333333 2.11333</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>23.333333338</td>
</tr>
</tbody>
</table>

Iwamoto_2000: control groups, combined effects and SDs

<table>
<thead>
<tr>
<th>Iwamoto_K2_2 control arms</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample (N)</td>
<td>20</td>
<td>29</td>
<td>49</td>
</tr>
<tr>
<td>Mean (M)</td>
<td>-0.79</td>
<td>0.38</td>
<td>-0.09755102</td>
</tr>
<tr>
<td>Standard Deviation(SD)</td>
<td>1.12</td>
<td>3.5</td>
<td>2.610953794</td>
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</table>

<table>
<thead>
<tr>
<th>Iwamoto_K2_3 control arms</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Combined 1+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>29</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>Mean</td>
<td>0.38</td>
<td>1.35</td>
<td>0.7874</td>
</tr>
<tr>
<td>SD</td>
<td>3.5</td>
<td>1.72</td>
<td>2.696769037</td>
</tr>
</tbody>
</table>

1+2                        | Group 3 | Combined +3 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Final for analysis</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Mean</td>
<td>0.7874</td>
<td>-0.79</td>
</tr>
<tr>
<td>SD</td>
<td>2.696769037</td>
<td>1.12</td>
</tr>
<tr>
<td>Final for analysis</td>
<td>70</td>
<td>2.222401472</td>
</tr>
</tbody>
</table>
Formula 2

Groups 1 and 2

Mean

\[ ES = \frac{M_1 + M_2}{2} \]

Combined effect size (ES)

\[ V = \frac{1}{4} \left( SD_1^2 + SD_2^2 + 2 \cdot r \cdot SD_1 \cdot SD_2 \right) \]

Combined Variance

Weight (WT)

\[ WT = \frac{1}{V} \]

Correlation-\( r \) (2 studies) 0.5

SD-combined

\[ SD = \sqrt{V} \]

Correlation between the groups

<table>
<thead>
<tr>
<th>Iwamoto_K2+D_2 control arms</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Effect size (ES)</th>
<th>Correlation-( r )</th>
<th>Variance</th>
<th>Weight (WT)</th>
<th>ES*WT</th>
<th>SD-combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>20</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.79</td>
<td>0.38</td>
<td>-0.205</td>
<td>0.5</td>
<td>4.3561</td>
<td>0.229563141</td>
<td>-0.04706</td>
<td>2.087127212</td>
</tr>
<tr>
<td>SD</td>
<td>1.12</td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Iwamoto_K2_3 control arms</th>
<th>Group 1</th>
<th>Group 2</th>
<th>ES</th>
<th>Correlation-( r )</th>
<th>Variance</th>
<th>Weight (WT)</th>
<th>ES*WT</th>
<th>SD-combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>29</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.38</td>
<td>1.35</td>
<td>0.865</td>
<td>0.5</td>
<td>5.3071</td>
<td>0.188426824</td>
<td>0.162989</td>
<td>2.303714392</td>
</tr>
<tr>
<td>SD</td>
<td>3.5</td>
<td>1.72</td>
<td></td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>1+2</th>
<th>Group 3</th>
<th></th>
<th>ES</th>
<th>Correlation-( r )</th>
<th>Variance</th>
<th>Weight (WT)</th>
<th>ES*WT</th>
<th>SD-combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>50</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.865</td>
<td>-0.79</td>
<td>0.0375</td>
<td>0.5</td>
<td>2.285415</td>
<td>0.437557287</td>
<td>0.016408</td>
<td>1.511758919</td>
</tr>
<tr>
<td>SD</td>
<td>2.303714392</td>
<td>1.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1+2</th>
<th>Group 3</th>
<th></th>
<th>Using Formula 1</th>
<th>Correlation-( r )</th>
<th>Variance</th>
<th>Weight (WT)</th>
<th>ES*WT</th>
<th>SD-combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>50</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.865</td>
<td>-0.79</td>
<td>0.392142857</td>
<td>0.5</td>
<td>2.285415</td>
<td>0.437557287</td>
<td>0.171585</td>
<td>1.511758919</td>
</tr>
<tr>
<td>SD</td>
<td>2.303714392</td>
<td>1.12</td>
<td>1.901166667</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure A3.2b. Examples of data extractions and estimations of standard deviations from the graphs as published in the original articles.

Example of data extraction: Fractures [article by Inoue et al (65), Figure 2 and Table 2]

Data taken from Fig 2, efficacy population table, because these numbers were further analyzed in Table 2

<table>
<thead>
<tr>
<th>136</th>
<th>Inoue 2009</th>
<th>No-fracture subgroup: K2+Calcium vs. Calcium Alone 1372 1381</th>
</tr>
</thead>
</table>

Calculations: All reported fractures are sum of new vertebral fractures (detected by Xrays, last FU 36 months, from Table 2) and all clinical fractures at 36 months.

Numbers of clinical fractures are estimated from incidence rates at 36 months given as #/100 person-years

Estimation of fractures

<table>
<thead>
<tr>
<th>No fracture subgroup</th>
<th>Fracture subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>K group</td>
<td>Calcium</td>
</tr>
<tr>
<td>Calcium</td>
<td>K group</td>
</tr>
<tr>
<td>Calcium</td>
<td>Calcium</td>
</tr>
<tr>
<td>Total # of patients</td>
<td>1372</td>
</tr>
<tr>
<td>1381</td>
<td></td>
</tr>
<tr>
<td>Patient years (PY) at 36 months</td>
<td>2770 2779</td>
</tr>
<tr>
<td>1094</td>
<td>1105</td>
</tr>
<tr>
<td>New vertebral fracture</td>
<td>76</td>
</tr>
<tr>
<td>71</td>
<td></td>
</tr>
<tr>
<td>VF Incidence (#/100 PY)</td>
<td>2.743682</td>
</tr>
<tr>
<td>2.554876</td>
<td>(New VF*100)/PY</td>
</tr>
<tr>
<td>13.80255941</td>
<td></td>
</tr>
<tr>
<td>13.755656</td>
<td></td>
</tr>
<tr>
<td>Clinical Fractures: Cumulative Incidence at 36 mons</td>
<td>1.3</td>
</tr>
<tr>
<td>1.30</td>
<td>Figure 3</td>
</tr>
<tr>
<td>Clinical fractures</td>
<td>36.01</td>
</tr>
<tr>
<td>36.127 (PY x Incidence) /100</td>
<td>24.068</td>
</tr>
<tr>
<td>29.835</td>
<td></td>
</tr>
<tr>
<td>All reported fractures (sum)</td>
<td>112.01</td>
</tr>
<tr>
<td>107.127</td>
<td></td>
</tr>
<tr>
<td>Sum: VF+clinical fractures</td>
<td>175.068</td>
</tr>
<tr>
<td>181.835</td>
<td></td>
</tr>
</tbody>
</table>

Example of data extraction: BMD [article by Knapen, Figure 2 (71)]

Explanation for measuring and calculations of LS BMD, mean and SD

<table>
<thead>
<tr>
<th>305</th>
<th>Knpen 2007</th>
<th>K2 vs. placebo</th>
<th>36 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated from Fig 2: distance from 0-1%=6mm</td>
<td>LSBMD</td>
<td>Placebo</td>
<td>K</td>
</tr>
<tr>
<td>Distance for each % change (6 mm)</td>
<td>6 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>164 161</td>
<td></td>
<td></td>
</tr>
<tr>
<td>measured distance for mean (mm)</td>
<td>0 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>0</td>
<td>0.166666667</td>
<td></td>
</tr>
<tr>
<td>measured distance for SE (mm)</td>
<td>2.5 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change (SE)</td>
<td>0.416666667 0.333333333</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change (SD)</td>
<td>5.335936865 4.229525847</td>
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</tbody>
</table>
Figure A3.3.  Posterior distributions of vitamin K2 effect on fractures: current and future studies. Red solid lines denote distributions for all clinical fractures, blue solid lines denote distributions for non-vertebral fractures, green solid lines denote distributions for vertebral fractures, purple solid lines denote distributions for hip and grey solid lines denote distributions for arm fractures.
8.3 Appendix 3: WinBUGS codes: Bayesian meta-analyses of continuous and binary outcomes by different priors on between-study variance

```plaintext
### WinBUGS code for continuous outcome: BMD model

#j indexes alternative prior distributions
for (j in 1:8) [
  mu[j] ~ dunif(-20, 20)
  new_mu[j] ~ dnorm (mu[j], inv.tau.sqrd[j])

  #probAny is probability of any effect, increase >0
  # step function: step (e) = 1 if e>=0; 0 otherwise.
  ProbAny_all_now[j]<-step(mu[j])
  ProbAny_all_new[j]<-step(new_mu[j])

  # probability that an increase in LS is 1% (similar to that with vitamin D and calcium)
  ProbGE1_now[j]<-step(mu[j] -0.5)
  ProbGE1_new[j]<-step(new_mu[j] -0.5)

  #k indexes study number
  for (k in 1:8) [
    theta[j, k] ~ dnorm(mu[j], inv.tau.sqrd[j])
    rtx[j, k] ~ dnorm(mu_t[j, k], prec_t[j, k])
    rtx[j, k] <- rt[k]
    prec_t[j, k]<- nt[k]/(sd_t[k]*sd_t[k])

    rcx[j, k] ~ dnorm(mu_c[j, k], prec_c[j, k])
    rcx[j, k] <- rc[k]
    prec_c[j, k]<- nc[k]/(sd_c[k]*sd_c[k])

    mu_t[j, k] <- theta[j, k] + mu_c[j,k]
    mu_c[j,k] ~ dunif(-20, 20)

    dev_t[j,k] <- 0.5*pow(rtx[j,k]-mu_t[j,k],2) / (pow(sd_t[k], 2)/ nt[k])
    dev_c[j,k] <- 0.5*pow(rcx[j,k]-mu_c[j,k],2) / (pow(sd_c[k], 2)/ nc[k])

    dev[j,k] <- dev_t[j,k] + dev_c[j,k]
  ]

  total.dev [j]<- sum(dev[j, 1:8])
]

# residual deviance for each j,k
```

k again indexes study number
for (k in 1:8)[
```
# variances & precisions:
s_t[k]<-(nt[k]-1)* sd_t[k] * sd_t[k]
s_c[k]<-(nc[k]-1)* sd_c[k] * sd_c[k]
sigma.sqrd[k] <- (((s_t[k] + s_c[k])/(nt[k] + nc[k]-2))* (1/(nt[k] + 1/nc[k])))
prec.sqrd[k] <- 1 / sigma.sqrd[k]

s0.sqrd <- 1 / mean(prec.sqrd[1:8])

# Prior 1: Gamma(0.001, 0.001) on inv.tau.sqrd
inv.tau.sqrd[1] ~ dgamma(0.001, 0.001)
tau[1] <- sqrt(tau.sqrd[1])

# Prior 2: Uniform(0, 3)
tau.sqrd[2] ~ dunif(0, 5)
tau[2] <- sqrt(tau.sqrd[2])

# Prior 3: Uniform(0, 3) on tau
tau[3] ~ dunif(0, 5)

# Prior 4: Uniform shrinkage on tau.sqrd
B0 ~ dunif(0, 1)
tau.sqrd[4] <- s0.sqrd * (1 - B0) / B0
tau[4] <- sqrt(tau.sqrd[4])

# Prior 5: Dumouchel on tau
D0 ~ dunif(0, 1)
tau[5] <- sqrt(s0.sqrd) * (1 - D0) / D0

# Prior 6: Half-Normal on tau.sqrd
p0 <- phi(0.75) / s0.sqrd
tau.sqrd[6] ~ dnorm(0, p0)I(0, )
tau[6] <- sqrt(tau.sqrd[6])

# Prior 7: Half-Normal on tau, var = 100, tau~ dnorm(0,0.01) I (0, )
tau[7]~ dnorm(0, 0.01)I(0, )

# Prior 8: Half-Normal on tau, var = 1, tau~ dnorm(0,1) I (0, )
tau[8]~ dnorm(0, 0.1)I(0, )
```r
```
for (k in 1:5) [# log-odds ratios:
  y[k] <- log((((rt[k] + 0.5) / (nt[k] - rt[k] + 0.5)) / ((rc[k] + 0.5) / (nc[k] - rc[k] + 0.5))))
  # variances & precisions:
  sigma.sqrd[k] <- 1 / (rt[k] + 0.5) + 1 / (nt[k] - rt[k] + 0.5) + 1 / (rc[k] + 0.5) + 1 / (nc[k] - rc[k] + 0.5)
  prec.sqrd[k] <- 1 / sigma.sqrd[k]
]
  s0.sqrd <- 1 / mean(prec.sqrd[1:5])
8.4 Appendix 3: List of ineligible articles


8.5 Appendix 4: Study protocol

Study Protocol (August 25, 2009)

The Effect of Vitamin K on Bone Health: A Systematic Review (Study Protocol)

BACKGROUND

Description of the condition

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, resulting in bone fragility and fractures (1). It affects one of six Canadian women aged 50 years and older (2). In addition, one of two Canadian women aged over 50 are diagnosed with low bone mass (osteopenia) (2), a condition that precedes osteoporosis. Osteoporotic fractures, the main clinical expression of osteoporosis, occur in both women with osteoporosis and women with osteopenia (3). Vertebral, hip and wrist fractures are the major types of osteoporotic fractures (4). The lifetime risk of any osteoporotic fracture for an average 50-year-old North American woman is over 40% (5). Osteoporotic fractures decrease quality of life, have high mortality and morbidity and are associated with considerable healthcare costs (6-8). For the primary prevention of osteoporosis in postmenopausal women aged over 50 years, current clinical guidelines recommend daily intake of 800 IU of vitamin D3 and 1000-1500 mg of calcium (9).

Description of the intervention

However, recent research suggests that vitamin K has beneficial effects on bone health. Vitamins K1 and K2 are two natural types of vitamin K (10): vitamin K1 (phylloquinone) is found in green leafy vegetables, herbs and green tea, while vitamin K2 (menaquinones: MK-4, MK-7) is synthesized by bacteria in the gastrointestinal tract and is found in fermented soy (e.g., natto) (11). Vitamin K2 converts to vitamin K1 in tissues (11).

How the intervention might work

Vitamin K is an essential cofactor for the carboxylation of glutamate to gamma-carboxyglutamic acid (Gla), which confers calcium-binding properties to vitamin K dependent proteins (10). The main vitamin K-dependent bone proteins, osteocalcin and matrix Gla protein, increase bone formation, bone mineralization and bone stiffness (12;13).

Why it is important to do this review

Evidence from epidemiologic studies suggests that vitamins K1 and K2 reduce bone loss and fracture risk (14). Seven Japanese randomized controlled trials (RCTs) and their classical meta-analysis 15 published in 2006 found that vitamin K2 significantly decreases the risk of vertebral and non-vertebral fractures by 60% and 81%, respectively. Since 2006, several RCTs including Caucasian populations have been released, showing a significant decrease of all clinical fractures with vitamin K1 but no effect on bone mineral density (BMD) (16-20).

Few controversies arise around the effect of vitamin K on bone health: 1) differences in the effect of vitamin K on BMD have been shown between Japanese and Caucasian studies: it has been protective of bone loss in elderly Japanese women (15) while it has had nil effect on BMD in postmenopausal Caucasians (17-20); 2) vitamin K has been associated with a high 55-80% relative risk reduction of osteoporotic and all clinical fractures in both Japanese and Caucasians (16). This risk reduction equals or is even better than that of pharmacologic therapy (21-25). Therefore, a new systematic review is required to evaluate the efficacy of vitamin K on BMD and fractures as independent and joint outcomes, in order to provide balanced and unbiased conclusions.
OBJECTIVES

Overall Research Question
“Does vitamin K affect bone outcomes in adults aged 40 years and older?”

Primary Research Objective
To determine the effect of vitamin K on incidence of all clinical fractures, non-vertebral fractures and vertebral fractures (clinical and morphometric), hip and wrist fractures in adults aged 40 years and older

Secondary Research Objectives
1) To determine whether vitamin K has an effect on bone mineral density (BMD), bone quality parameters, bone strength parameters and bone turnover markers in adults aged 40 years and older.
2) To predict the effect of vitamin K on the risk of all and specific types of fractures in a new trial;
3) To determine the effect of vitamin K on joint bone outcomes, fractures and BMD;
4) To explore whether important covariates such as age, comorbidities, prior fractures, vitamin D and calcium intake significantly change the efficacy of vitamin K on fractures and BMD as independent and joint outcomes.

METHODS

Criteria for considering studies for this review
Types of studies
We will include all published and unpublished (26) comparative observational (retrospective and prospective cohort studies and case-control) and experimental studies (RCTs with individually randomized participants, quasi-randomized controlled trials or before-after trials) without any language restrictions that reported the effect of vitamin K (supplementation or dietary intake) on bone outcomes. The cross-sectional designs without control groups may be considered in sensitivity analysis. We will exclude cluster-randomized trials, descriptive studies including case series or case reports, reviews, and letters, editorials or commentaries without original data.

Types of participants
We will include studies done in individually randomized/observed women and men aged 40 years and older.

Types of interventions
We will compare the effect of vitamin K1 (phyloquinone) or vitamin K2 (menaquinones, MK-4 and MK-7) to placebo, control (e.g., vitamin D, calcium, bone antiresorptive therapies, educational interventions) or no treatment.

Types of outcome measures
Primary outcome
Our primary outcome will be all clinical fractures, vertebral (clinical or morphometric) and all non-vertebral fractures, hip and wrist fractures.

Secondary Outcomes
Our secondary outcomes are:
1) Mean absolute (g/cm2) and relative (%) changes in BMD of the femoral neck, lumbar spine (L1-L4, L2-L4), total hip or radius (proximal, distal and ultradistal radius) at 12 months or later. A clinically significant decrease in BMD will be defined at 3% 21;27.

2) Mean changes from baseline in the bone quality parameters measured by peripheral or central quantitative computer tomography including cortical thickness (mm), trabecular thickness (mm), trabecular number and trabecular spacing (mm–1), cortical and trabecular volumetric BMD (g/cm3);

3) Mean changes in cross-sectional bending stiffness of a long bone (Nm2) - a bone strength parameter that determines mechanical properties of the bone (measured by mechanical response tissue analyzer-MRTA);

4) Mean changes in bone turnover markers: 1) bone formation markers: procollagen type 1 N-terminal propeptide (P1NP), osteocalcin (OC) and bone specific alkaline phosphatase (BAP); and, 2) bone resorption markers: hydroxyproline, pyridinoline (PYD), deoxypyridinoline (DPD), and type 1 collagen cross linked N-and C- telopeptides (NTX and CTX).

Search methods for identification of studies
We will search without language restrictions for all publications on vitamins K1 and K2 between January 1950 and August 2009, using electronic databases, Medline (1950 - ), EMBASE and Classical EMBASE (1947 - ), Cochrane Controlled Clinical Trials Register (CENTRAL), the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), International Pharmaceutical Abstracts (1970- ), Current Content, Cumulative Index to Nursing and Allied Health Literature (CINAHL, 1980-), Allied and Complimentary Medicines (AMED, 1985 - ) and International Bibliographical Information on Dietary Supplements (IBIDS, 1986-). We will also search other electronic sources such as bone conference proceedings databases (e.g., the American Society of Bone and Mineral Research at URL: www.asbmr.org), and dissertation databases, including Foreign Doctoral Dissertations (URL: http://www.crl.edu) North American Proquest Database of Dissertations and Theses (URL: http://proquest.umi.com) and Thesis Canada Portal (URL: http://www.collectionscanada.gc.ca /thesescanada).

Bibliographies of original studies or reviews, and major osteoporosis, nutrition, epidemiologic and general medicine journals (e.g., Osteoporosis Int, J Bone Miner Res, Calified Tissue Int, Bone, Am J Clin Nutr, Am J Nutr, Am J Epi, New Engl J Med, Lancet, JAMA and BMJ) will be hand-searched to find additional articles.

We will employ comprehensive and non-restrictive search strategies, developed with an information specialist (Mr. Panos Lambiris), to identify potentially eligible studies. We will combine the following MeSH terms as subject headings or text words: “vitamin K”, “phylloquinone”, “menaquinone”, “MK-4”, “MK-7”, “farnoquinone” “naphthoquinone”, “konakion”, “phytonadione”, “menadione”, “menadiol”, “mephyton”, “phytomenadione”, “aquamephyton”, “menatetrenone”, fracture, bone”, “bone and bones”, “bone diseases”, “osteoporosis”, “bone density” and other bone-related terms (Fig1).

Reporting of the findings will be in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement (e.g., Fig 2) 28.

Study selection
Stage 1- Title and abstract
One reviewer (Olga Gajic-Veljanoski - OGV) will assess titles and abstracts to identify potentially relevant articles.

Stage 2- Full review
All selected articles will be reviewed in full by two reviewers (Angela Cheung - AC and OGV) and will be included in analysis if they satisfy the following criteria:

a) One of the primary or secondary outcomes are reported; and,
b) Vitamins K1 and K2 are identified as an intervention or exposure.

Reasons for exclusion and data on excluded studies will be kept in reference manager databases.

**Assessment of risk of bias in included studies**

Quality assessments will be done independently by two reviewers (OGV, AC). Disagreements will be resolved by consensus. The level of agreement between reviewers will be quantified using a \( \kappa \) statistic, ranging from +1 (perfect agreement) to −1 (complete disagreement). If consensus cannot be reached, we will seek an opinion from the third reviewer. We will also contact primary authors to clarify incomplete information.

We will the Quality Index, a 27-item checklist designed by Downs and Black (1998) (29), to assess the quality of observational studies. This checklist was recommended among 14 “best” study quality instruments and was mostly used in systematic reviews of observational studies (30). This tool was designed to tap five domains of study quality: reporting (10 items), external validity (3 items), bias (7 items), confounding (6 items) and study power (1 item). This scale has high internal consistency (the Kuder-Richardson formula 20 (K-R 20) =0.89), good test-retest (r=0.88) and inter-rater reliability (r=0.75) and good face and criterion validity. It takes 20 minutes to complete with a maximum score of 32. We will modify the Quality Index to reflect the topic, bias and studies included in our review.

Experimental studies will be assessed with an 11-item checklist developed by the Cochrane Collaboration Back Review Group for the quality assessment of RCTs, controlled clinical trials and crossover studies (31). It examine presence of selection bias (randomization, treatment allocation–3 items), performance bias (blinding, co-interventions, compliance – 4 items), detection bias (outcome assessment–2 items) and attrition bias (loss to follow up, intention-to-treat analysis–2 items). It takes 10 minutes to complete and the maximum score is 11. We will also include 2 items related to the completeness of outcome data and selective reporting of findings from the Cochrane risk of bias checklist (32).

To both checklists, we will add topic-specific items regarding timing of BMD measurement, history of fractures and baseline measurement of morphometric vertebral fractures, and risk of bias due to regression to the mean (27). Each study will be categorized in one of 3 risk of bias categories (i.e., low, unclear, high risk of bias) (32).

**Data extraction**

We extracted information on year of publication, country of origin, clinical setting, trial duration, participant demographics (e.g., age, sex and, ethnicity) and dwelling (community vs. nursing home), bodyweight or body mass index, sample size, vitamin K types and doses, additional supplementation with calcium and vitamin D, calcium and vitamin D doses, baseline calcium, vitamin D and vitamin K intake, serum 25-(OH)-vitamin D3 concentration, type of control treatment (placebo or control drug), use of bone sparing drugs, comorbidities, compliance (high compliance is defined as use of study drugs by at least 80% participants), mobility and physical activity, baseline BMD, baseline fracture risk (defined by history of prior fractures and prevalence of fractures in control group), loss-to-follow-up (see Table 1). We will collect information on outcomes: type and number of new fractures, mean bone density BMD including SD bone mineral content (g/cm2) or bone mineral content ± SD (g/cm3), site (femoral neck, lumbar spine (L1-L4, L2-L4, or other), trochanter, Ward’s triangle, total hip, proximal, distal or
ultradistal radius), and BMD machine (DXA or other), frequency of measurements and reported coefficient of variation (CV).

These variables have been pre-specified based on their biological plausibility (e.g., age, comorbidities, type, dose and duration of vitamin K treatment), known risk for osteoporosis (e.g., females, institutional settings, history of previous fractures, vitamin D and calcium intakes, mobility) or their potential to affect validity of study findings (e.g., sample size, compliance, type of BMD machine and frequency of measurements, trial duration).

We will collect the information in Data Abstraction Forms that will be pilot-tested in for completeness, preciseness and feasibility using a random sample of several observational and experimental studies to test. All data will be stored in databases (e.g., Microsoft Office Access or Excel).

Data will be extracted independently by two reviewers (OGV, AC). Disagreements will be resolved by consensus. Authors will be contacted if further study details are needed, discrepancies or inaccuracies are detected, or duplicate publication is suspected.

**STATISTICAL ANALYSIS**

**Measures of treatment effect**

We will use relative risk/risk ratio (RR) to measure the effect of vitamin K on the primary binary outcome, fractures. A RR of 1.0 or less will indicate a lower risk of fractures in patients on vitamin K. Bayesian meta-analysis will combine all types of study designs and thus, will measure the treatment effect using odds ratio (OR). The ORs will be transformed to log-odds ratios by taking natural logarithm of the ORs. Log-odds ratios are approximately normally distributed and are easier to combine (33). As fractures are rare outcome, we could assume that RR and OR are approximately the same. We will apply the continuity correction (i.e., adding 0.5 to each treatment cell) before calculating RR/ORs if any treatment arm has zero fracture events (33). All our secondary outcomes are continuous variables, and thus, the mean difference (MD) will be used to measure effect size. In Bayesian bivariate analysis, we will use MD to measure the effect of vitamin K on joint outcomes, fractures and BMD.

**Unit of analysis issues**

We will include studies with individually randomized patients. We expect to find differences in reporting BMD measurements including SDs (e.g., reporting of standard errors instead of SDs) and to contact primary authors to resolve data inaccuracies.

**Assessment of heterogeneity**

We will use Cochran’s Q test (Cochran’s Chi-Square test of homogeneity) to detect statistical heterogeneity and will increase a significance threshold to p < 0.1 since the test has low statistical power (33;34). We will use I² statistic, which indicates the proportion of variability across studies due to heterogeneity beyond chance, to quantify heterogeneity (I² statistic > 75% was considered substantial) (33;34).

**Assessment of reporting biases**

We will explore publication bias using funnel plots and the Egger’s regression model (33;34). If publication bias is detected, its effect on study findings will be examined using the fail-safe number method (35-37). The fail-safe number is the number of unpublished studies that would be needed to nullify the observed result to statistical non-significance at α level= 0.05 (35-37). Publication bias is substantial if the fail-safe number is less than 5n+10, where n is the number of studies included in the meta-analysis (35-37).
Data synthesis

Meta-analyses and meta-regressions will be done using the Cochrane Collaboration software - Review Manager (RevMan 5) (38), WinBUGs, R and STATA. Tests of significance will be 2-sided and regarded as statistically significant if \( p < 0.05 \). Forest and meta-regression plots will be used to present study findings. Four types of statistical analyses will be performed to answer the research objectives.

1) Classical univariate random effects meta-analysis to examine the independent effect of vitamin K on the primary and secondary bone outcomes. The fixed effects model assumes that each observed individual study result is estimating a common unknown overall pooled effect while the random effects model assumes that each individual observed study result is estimating its own unknown underlying effect, which in turn are estimating a common population mean (33). Therefore, the random effects model allows for the existence of between-study heterogeneity as well as the within-study variability (33). The sDerSimonian and Laird random effects model accounts for between-study variability using the general inverse weighted variance method (39). Since clinical heterogeneity is expected due to substantial differences in patient demographics and clinical history, we will use the sDerSimonian and Laird random effects model to meta-analyze the primary and secondary outcomes (33;34;39). We will calculate the risk ratios (RRs) for the primary outcomes and the mean difference (MD) for the secondary outcomes including their 95% confidence intervals (CIs).

We will separately analyze data from experimental and observational studies.

2) Bayesian univariate and bivariate random-effects meta-analyses and general evidence synthesis (including various sources of data) will be used to analyze:
- The effect of vitamin K on fractures and BMD, as independent and joint outcomes
- The effect of vitamin K on fracture risk reduction in a “new trial”

A Bayesian meta-analytic approach has several advantages over the classical method:
1) It allows for greater uncertainty than the classical approach by allowing that both the overall population effect and the between-study variance be estimated by the data (40;41). This is based on an assumption of exchangeability between the relative efficacies underlying the trials (i.e., borrowing strength) (40;41);
2) It provides direct probability estimates of treatment effectiveness;
3) It can be used to calculate the treatment effect for a “new study”;
4) It relaxes the assumption of the classical approach that heterogeneity between similar sets of trials is equal (40;41). This is important if a small number of trials are meta-analyzed: in this case, it is difficult to obtain a good estimate of the heterogeneity, and thus, it is difficult to account for the heterogeneity properly when pooling the trials (40;41);
5) It allows synthesizing different sources of data (e.g., observational studies, before-after studies) to estimate the overall treatment effect (i.e., the general synthesis of evidence method) (41;45-47).

We will employ hierarchical univariate random-effects meta-analysis (URMA) to determine the effect of vitamin K on the risk of fractures by sampling mean population log-odds and ORs from the posterior distributions of the observed data. The probability of high (OR\( \leq 0.2 \)), moderate (0.2<OR\( \leq 0.5 \)) and low (0.5<OR\( \leq 0.8-1 \)) risk reduction will be calculated.
We will calculate the effect of vitamin K on fractures in a “new study” using Markov chain Monte Carlo (MCMC) simulations, and borrowing strength from the existing data (40;41). The “new study” log-odds and ORs will be obtained through sampling from the posterior distributions of the observed log-odds that include some normal error. The additional variability in the “new study OR” will indicate a degree of uncertainty that remains in the effectiveness of vitamin K for fracture prevention, given that the observed effect is not constant across included studies.

We will perform Bayesian bivariate random-effects meta-analysis (BRMA) to assess the effect of vitamin K on BMD and fractures as joint outcomes (42-44). The classical bivariate random-effects meta-analysis models correlated end-points, requiring the within-study correlation to be “known” or zero (unlike in the case of structurally dependent endpoints) (42-44). The Bayesian BRMA models the overall correlation of joint outcomes (i.e., the within and between-study correlation altogether) and estimates the “known” within-study correlation from the joint posterior distributions. These correlations are necessary to obtain to estimate the joint effect of vitamin K on fractures and BMD and calculate MD.

**Generalized evidence synthesis**

We will include all types of comparative studies such as observational studies in the review and will examine changes in the effectiveness of vitamin K for fracture reduction when observational evidence is not completely ignored. Generalized evidence synthesis is a method that includes data from different sources such as observational, using two approaches (41;45-47):

1) Approach 1 – Power transform prior, which downweights observational likelihood (data) to form an informative prior for RCTs;
2) Approach 2 – Bias allowance model, which is a hierarchical model that pools all available data but it acknowledges bias coming from observational studies by including direct estimates of the possible extent of bias (e.g., the extent of bias in observational evidence of effectiveness ranges from ±30 to ±100% 48-50). This is an extension of random effects model, which changes from 2-level to a 3-level model. It has an extra level of variation to allow for variability in effect sizes between different sources of evidence (i.e., assigned to each study design: RCT, case-control, cohort), on top of variability between study estimates within each study design.
3) Indirect and mixed treatment comparisons (MTC) to establish the relative effect of vitamin K to vitamin D and calcium in absence of trials including head-to-head comparisons

We will use indirect and mixed treatment comparisons (MTC) within a random-effects model to estimate relative effectiveness of vitamin K to vitamin D and calcium if no direct or head-to-head RCTs are found (51-55).

In MTC, we calculate direct and indirect treatment effects as following: we obtain the direct effect $d(AB)$ in a trial which compares A (Vitamin K) to B (vitamin D plus calcium). If there is no direct comparisons, we can calculate an indirect estimate of $d(AB)$ from trials that compare A to C (placebo) and B to C by making assumption that $d(BC) - d(AC) = d(AB)$ (51-55). MTC analysis requires for each treatment to have a chain of pair-wise comparisons that connects it to every other treatment (51-55).

Indirect comparisons estimate treatment effect without breaking randomisation (51-55). The major assumption is that treatment effects are drawn from a common study population (e.g., not varying with disease severity, for example baseline fracture risk) (51;54;55). This could be tested by including a significant covariate in the model.

4) Subgroup analysis and Bayesian meta-regression to explore whether important confounders significantly change the efficacy of vitamin K on fractures and BMD
We will perform subgroup analyses to examine clinical heterogeneity of included studies and to explore whether the treatment effect (e.g., reduction in fracture risk) of vitamin K is modified by clinical, demographic or other variables. We have a priori defined a list of 18 variables (see Table 1): ethnicity, clinical setting, vitamin K type, dose and duration, age, sex, bodyweight, dwelling, additional supplementation with calcium and vitamin D including doses, baseline calcium, vitamin D and vitamin K intakes, serum 25-(OH)-vitamin D3 concentration, use of bone sparing drugs, comorbidities, compliance, mobility and physical activity, baseline BMD and baseline fracture risk (defined by history of prior fractures and prevalence of fractures in control group).

Meta-regression will be used to assess the effect of ethnicity, age, baseline fracture risk, bodyweight, baseline vitamin D and calcium intake, comorbidities, trial duration and compliance on treatment efficacy. A number of variables that will be included in meta-regression will depend on the number of vitamin K studies and statistical significance of specific covariates in subgroup analyses.

Dealing with missing data

Classical meta-analysis
In case of missing or inaccurate original data, we will contact the primary authors. If we are unable to obtain this information, and if missingness is not larger than 5%, we will impute data using a rule of thumb proposed by Harrell (56). Sensitivity analysis will be performed to test the influence of missing data on study findings.

Bayesian meta-analysis
The Bayesian meta-analytic approach naturally deals with missing data as it borrows strength from all observed data and imputes missing information using MCMC.

Sensitivity analysis
The effect of individual studies on the pooled effect size will be assessed with influence analysis, in which the analysis was repeated omitting one study at a time, to examine how much each study modifies the pooled effect size.

We will explore the effect of bias (low quality studies vs. high quality studies) and missing data on model estimates in both classical and Bayesian meta-analyses (e.g., models with imputed data will be compared to models including missing data and to models excluding missing data).

APPENDICES

Figure 1. Search Strategies in Medline, Embase, Embase Classic, AMED, International Pharmaceutical Abstracts Database, CINAHL
Figure 2. QUOROM trial flow diagram: Study selection
Table 1. Data extraction and subgroup analyses: Variables
Figure 1. Search Strategies in Medline, Embase, Embase Classic, AMED, International Pharmaceutical Abstracts Database, CINAHL

MEDLINE-Aug 20, 2009
Database: Ovid MEDLINE(R) <1950 to August Week 2 2009>
Search Strategy:

1   exp Vitamin K/ (8427)
2   vitamin k*.mp. (12043)
3   menaquinone*.mp. (1449)
4   mk-4.mp. (111)
5   mk-7.mp. (367)
6   phyloquinone*.mp. (489)
7   konakion*.mp. (38)
8   phytonadione*.mp. (83)
9   menadione*.mp. (2094)
10  aquamephyton*.mp. (2)
11  menadiol*.mp. (77)
12  mephyton*.mp. (4)
13  phytomenadione*.mp. (33)
14  menatetrenone*.mp. (200)
15  exp vitamin K deficiency/ (1777)
16  or/1-15 (14084)
17  exp "Bone and Bones"/ (406188)
18  exp Fractures, Bone/ (114614)
19  exp Bone Diseases/ (336624)
20  exp Musculoskeletal Physiological Phenomena/ (605416)
21  bone*.mp. (565685)
22  osteo*.mp. (263999)
23  or/17-22 (1475104)
24  23 and 16 (1272)
25  exp dietary supplements/ (22639)
26  exp food,fortified/ (6332)
27  25 or 26 (28562)
28  27 and 16 (136)
29  28 or 24 (1349)

****************************
EMBASE-Aug 20, 2009

Database: EMBASE <1980 to 2009 Week 33>

Search Strategy:

1 exp Vitamin K/ (11196)
2 vitamin k*.mp. (9193)
3 menaquinone*.mp. (1514)
4 mk-4.mp. (103)
5 MK-4*.mp. (1189)
6 MK-7*.mp. (592)
7 phylloquinone*.mp. (408)
8 konakion*.mp. (303)
9 phytonadiione*.mp. (79)
10 menadione*.mp. (3844)
11 aquamephyton*.mp. (56)
12 menadiol*.mp. (133)
13 mephyton*.mp. (26)
14 phytomenadione*.mp. (2228)
15 menatetrenone*.mp. (307)
16 farnoquinone*.mp. (385)
17 exp vitamin K deficiency/ (955)
18 or/1-17 (15687)
19 exp bone/ (222149)
20 exp bone fragility/ or exp bone metabolism/ or exp iliac bone/ or exp bone age/ or exp long bone/ or exp bone remodeling/ or exp "bone characteristics and functions"/ or exp bone dysplasia/ or exp bone turnover/ or exp bone density/ or exp bone structure/ or exp cortical bone/ or exp cancellous bone/ or exp bone densitometry/ or exp metatarsal bone/ or exp pubic bone/ or exp involutional bone loss/ or exp metacarpal bone/ or exp endocrine bone disease/ or exp metabolic bone disease/ or exp bone deformation/ or exp bone regeneration/ or exp bone strength/ or exp coccygeal bone/ or exp alkaline phosphatase bone isoenzyme/ or exp bone demineralization/ or exp carpal bone/ or exp bone mineral/ or exp bone disease/ or exp metacarpal bone fracture/ or exp bone/ or exp bone tissue/ or exp trabecular bone/ or exp bone mass/ or exp bone mineralization/ (495484)
21 exp fracture/ (85781)
22 exp bone disease/ (338566)
23 corticosteroid induced osteoporosis/ or idiopathic osteoporosis/ or osteoporosis/ or postmenopause osteoporosis/ or posttraumatic osteoporosis/ or primary osteoporosis/ or secondary osteoporosis/ or senile osteoporosis/ (44318)
24 22 or 21 or 23 or 20 (495484)
25 bone*.mp. (462992)
26 osteo*.mp. (220199)
27 25 or 24 or 26 (713351)
28 exp supplementation/ or exp diet supplementation/ or exp vitamin supplementation/ (70255)
29 28 and 18 (865)
30 18 or 29 (15687)
31 27 and 30 (1518)

********************************************************************
EMBASE CLASSIC PLUS EMBASE-Aug 20, 2009

Database: EMBASE Classic+EMBASE <1947 to 2009 Week 33>
Search Strategy:

1 exp Vitamin K/ (14215)
2 vitamin k*.mp. (11193)
3 menaquinone*.mp. (1617)
4 mk-4.mp. (109)
5 MK-4*.mp. (1409)
6 MK-7*.mp. (612)
7 phylloquinone*.mp. (468)
8 konakion*.mp. (383)
9 phytonadione*.mp. (106)
10 menadione*.mp. (5429)
11 aquamephyton*.mp. (81)
12 menadiol*.mp. (320)
13 mephyton*.mp. (48)
14 phytomenadione*.mp. (2936)
15 menatetrenone*.mp. (313)
16 farnoquinone*.mp. (444)
17 exp vitamin K deficiency/ (1140)
18 or/1-17 (19511)
19 exp bone/ (359091)
20 exp bone fragility/ or exp bone metabolism/ or exp iliac bone/ or exp bone age/ or exp long
bone/ or exp bone remodeling/ or exp "bone characteristics and functions"/ or exp bone dysplasia/
or exp bone turnover/ or exp bone density/ or exp bone structure/ or exp cortical bone/ or exp
cancellous bone/ or exp bone densitometry/ or exp metatarsal bone/ or exp pubic bone/ or exp
involutional bone loss/ or exp metacarpal bone/ or exp endocrine bone disease/ or exp metabolic
bone disease/ or exp bone deformation/ or exp bone regeneration/ or exp bone strength/ or exp
coccygeal bone/ or exp alkaline phosphatase bone isoenzyme/ or exp bone demineralization/or
exp carpal bone/ or exp bone mineral/ or exp bone disease/ or exp metacarpal bone fracture/ or
exp bone/ or exp bone tissue/ or exp trabecular bone/ or exp bone mass/ or exp bone
mineralization/ (691734)
21 exp fracture/ (113832)
22 exp bone disease/ (446596)
23 corticosteroid induced osteoporosis/ or idiopathic osteoporosis/ or osteoporosis/ or
postmenopause osteoporosis/ or posttraumatic osteoporosis/ or primary osteoporosis/ or
secondary osteoporosis/ or senile osteoporosis/ (49972)
24 22 or 21 or 23 or 20 (691734)
25 bone*.mp. (582751)
26 osteo*.mp. (274145)
27 25 or 24 or 26 (953026)
28 exp supplementation/ or exp diet supplementation/ or exp vitamin supplementation/ (76595)
29 28 and 18 (882)
30 18 or 29 (19511)
31 27 and 30 (1651)

***************************************************************************
Database: AMED (Allied and Complementary Medicine) <1985 to August 2009>
Search Strategy:

1. exp Vitamin K/ (24)
2. vitamin k*.mp. (42)
3. konakion*.mp. (1)
4. phytonadione*.mp. (1)
5. exp bone fragility/ or exp bone metabolism/ or exp iliac bone/ or exp bone age/ or exp long bone/ or exp bone remodeling/ or exp "bone characteristics and functions"/ or exp bone dysplasia/ or exp bone turnover/ or exp bone density/ or exp bone structure/ or exp cortical bone/ or exp cancellous bone/ or exp bone densitometry/ or exp metatarsal bone/ or exp pubic bone/ or exp involutional bone loss/ or exp metacarpal bone/ or exp endocrine bone disease/ or exp metabolic bone disease/ or exp bone deformation/ or exp bone regeneration/ or exp bone strength/ or exp coccygeal bone/ or exp alkaline phosphatase bone isoenzyme/ or exp bone demineralization/ or exp carpal bone/ or exp bone mineral/ or exp bone disease/ or exp metacarpal bone fracture/ or exp bone/ or exp bone tissue/ or exp trabecular bone/ or exp bone mass/ or exp bone mineralization/ (5253)
6. exp bone disease/ (4631)
7. corticosteroid induced osteoporosis/ or idiopathic osteoporosis/ or osteoporosis/ or postmenopausal osteoporosis/ or posttraumatic osteoporosis/ or primary osteoporosis/ or secondary osteoporosis/ or senile osteoporosis/ (832)
8. bone*.mp. (5946)
9. osteo*.mp. (6441)
10. vitamin k/ or vitamin k 2/ or vitamin k 3/ (24)
11. 4 or 1 or 3 or 10 or 2 (42)
12. 8 or 6 or 7 or 9 or 5 (13104)
13. 11 and 12 (11)

**************************************************
International Pharmaceutical Abstracts – Aug 20, 2009

Ovid Technologies, Inc. Email Service

Database: International Pharmaceutical Abstracts <1970 to August 2009>
Search Strategy:

1 vitamin k*.mp. (705)
2 menaquinone*.mp. (16)
3 mk-4.mp. (1)
4 MK-4*.mp. (72)
5 MK-7*.mp. (21)
6 phyloquinone*.mp. (13)
7 konakion*.mp. (25)
8 phytonadione*.mp. (189)
9 menadione*.mp. (76)
10 aquamephyton*.mp. (11)
11 menadiol*.mp. (15)
12 mephyton*.mp. (7)
13 phytomenadione*.mp. (15)
14 menatetrenone*.mp. (23)
15 farnoquinone*.mp. (0)
16 corticosteroid induced osteoporosis/ or idiopathic osteoporosis/ or osteoporosis/ or postmenopause osteoporosis/ or posttraumatic osteoporosis/ or primary osteoporosis/ or secondary osteoporosis/ or senile osteoporosis/ (1828)
17 bone*.mp. (4989)
18 osteo*.mp. (4565)
19 bone disease (534)
20 or/1-15 (906)
21 or/16-19 (8087)
22 20 and 21 (36)

*****************************************************************************
Figure 2. QUOROM trial flow diagram: Study selection

3080 references identified from bibliographic searches

N duplicates excluded

N abstracts assessed

N studies excluded (Reasons:)

N studies reviewed in full

N studies failed to meet inclusion criteria, reasons ref

N studies included in analysis ref
Table 1. Data extraction and subgroup analyses: Variables

<table>
<thead>
<tr>
<th>Variable Description</th>
<th>Type</th>
<th>Format</th>
</tr>
</thead>
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<td>year of publication</td>
<td>Continuous</td>
<td>YY</td>
</tr>
<tr>
<td>country of origin</td>
<td>Nominal</td>
<td>Look-up:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA Canada</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Japan England</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Germany</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>clinical setting</td>
<td>Binary</td>
<td>Ambulatory</td>
</tr>
<tr>
<td>trial duration</td>
<td>Continuous</td>
<td>##, months</td>
</tr>
<tr>
<td>Mean age ± SD, median (min-max)</td>
<td>Continuous</td>
<td>##, years</td>
</tr>
<tr>
<td>% Females</td>
<td>Continuous</td>
<td>0-100 %</td>
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<td>missing</td>
</tr>
<tr>
<td>Ethnicity/Race (majority)</td>
<td>Nominal</td>
<td>Look-up:</td>
</tr>
<tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Black</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
</tr>
<tr>
<td>Dwelling</td>
<td>Binary</td>
<td>Community</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nursing home</td>
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<td>Bodyweight, mean, median, SD, min, max</td>
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<td>##, kg</td>
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<td>##, kg/m2</td>
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<td>###### subjects</td>
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<td>Continuous</td>
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<td>Co-intervention with calcium and vitamin D</td>
<td>Binary</td>
<td>Yes/no</td>
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<td>If yes, Calcium and vitamin D dose</td>
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<td>Calcium, mg/day</td>
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<td>Baseline vitamin D intake, mean, median, SD, min, max</td>
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<td>### mg/day</td>
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<tr>
<td>Baseline calcium intake, mean, median, SD, min, max</td>
<td>Continuous</td>
<td>### IU/day</td>
</tr>
<tr>
<td>Baseline vitamin K intake, mean, median, SD, min, max</td>
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<td>### mcg/day</td>
</tr>
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<td>Serum 25-(OH)-vitamin D3 concentration, mean, median, SD, min, max</td>
<td>Continuous</td>
<td>### nmol/l</td>
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<td>Control treatment</td>
<td>Categorical</td>
<td>Look-up:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
</tr>
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<td>Vitamin D only</td>
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<tr>
<td></td>
<td></td>
<td>Calcium only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitamin D combined with calcium</td>
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<tr>
<td></td>
<td></td>
<td>Education</td>
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</tr>
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<td></td>
<td></td>
<td>Other</td>
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<tr>
<td>Use of bone sparing drugs</td>
<td>Binary</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Binary</td>
<td>Yes/no</td>
</tr>
<tr>
<td>If yes, type</td>
<td>Text</td>
<td></td>
</tr>
<tr>
<td>Mobility and physical activity</td>
<td>Categorical</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Parameter</td>
<td>Type</td>
<td>Category</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Baseline BMD, mean, SD, T score</td>
<td>Continuous</td>
<td>Continuous</td>
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<tr>
<td>Baseline fracture risk, %</td>
<td>Continuous</td>
<td>0-100 %</td>
</tr>
<tr>
<td>% Followed till the end</td>
<td>Continuous</td>
<td>0-100 %</td>
</tr>
<tr>
<td>% Followed till the end</td>
<td>Continuous</td>
<td>missing</td>
</tr>
<tr>
<td>Fractures, type</td>
<td>Categorical</td>
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</tr>
<tr>
<td>Fractures, number</td>
<td>Count</td>
<td>## for each type, by treatment group</td>
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<tr>
<td>BMD, mean, SD</td>
<td>Count</td>
<td>Mean ±SD</td>
</tr>
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<td>Nominal</td>
<td>Annual</td>
</tr>
<tr>
<td>Frequency of measurements</td>
<td>Categorical</td>
<td>Biannual, etc.</td>
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<tr>
<td>coefficient of variation (CV) reported, %</td>
<td>Continuous</td>
<td>0-100 %</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
References (pertinent to the Study Protocol [August 25, 2009])


Ref Type: Serial (Book,Monograph)


9. Chapter 4: Appendices

9.1 Appendix 1: Tables
Table A4.1: Data sources for BRMAs on BMD at the lumbar spine and all fractures: Vitamin K2 and vitamin K1

### VITAMIN K2

<table>
<thead>
<tr>
<th>Author_year</th>
<th>N</th>
<th>rt_bin</th>
<th>nt_bin</th>
<th>rc_bin</th>
<th>nc_bin</th>
<th>rt_cont</th>
<th>sd_t</th>
<th>nt_cont</th>
<th>rc_cont</th>
<th>sd_c</th>
<th>nc_cont</th>
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<tr>
<td>Inoue_1_2009</td>
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<td>112</td>
<td>1372</td>
<td>107</td>
<td>1381</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
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<tr>
<td>Inoue_2_2009</td>
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<td>175</td>
<td>627</td>
<td>181</td>
<td>635</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
</tr>
<tr>
<td>Iwamoto_2000_2001</td>
<td>4</td>
<td>2</td>
<td>23</td>
<td>6</td>
<td>24</td>
<td>0.90</td>
<td>2.11</td>
<td>22</td>
<td>0.38</td>
<td>3.37</td>
<td>29</td>
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<tr>
<td>Shiraki_2000</td>
<td>5</td>
<td>14</td>
<td>91</td>
<td>35</td>
<td>99</td>
<td>-0.50</td>
<td>10.95</td>
<td>105</td>
<td>-3.20</td>
<td>9.35</td>
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<td>Ushiroyma_2002</td>
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<td>Missing</td>
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<td>0.14</td>
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<td>Missing</td>
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<td>Kanpen_2007</td>
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<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
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<td>5.36</td>
<td>164</td>
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<td>Emaus_2010</td>
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<td>Missing</td>
<td>Missing</td>
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<td>-0.45</td>
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<td>Purwosunu_2006</td>
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<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>1.74</td>
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<td>1.33</td>
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<td>Binkley_2009</td>
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<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>-0.32</td>
<td>4.34</td>
<td>126</td>
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<td>3.10</td>
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</table>

### VITAMIN K1

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<th>nc_bin</th>
<th>rt_cont</th>
<th>sd_t</th>
<th>nt_cont</th>
<th>rc_cont</th>
<th>sd_c</th>
<th>nc_cont</th>
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</thead>
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<td>Cheung_2008</td>
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<td>37</td>
<td>217</td>
<td>44</td>
<td>223</td>
<td>-1.29</td>
<td>3.50</td>
<td>217</td>
<td>-1.22</td>
<td>2.90</td>
<td>223</td>
</tr>
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<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>-0.32</td>
<td>4.30</td>
<td>126</td>
<td>0.55</td>
<td>3.10</td>
<td>129</td>
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<td>4.90</td>
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<td>22</td>
<td>0.13</td>
<td>2.30</td>
<td>27</td>
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</tbody>
</table>

N denotes a number of studies included in the meta-analyses; rt-bin and rc_bin denote numbers of fractures in vitamin K and control groups, respectively, nt_bin and nc_bin denote the sample sizes of vitamin K and control groups, respectively; rt_cont, sd_t and nt_cont denote mean % change in BMD, standard deviation (%) and a sample size for a vitamin K group; rc_cont, sd_c and nc_cont are the corresponding symbols for a control group.
Table A4.2. Data extracted from 14 bisphosphonate trials to improve estimation of the between-study correlation

<table>
<thead>
<tr>
<th>N</th>
<th>First Author</th>
<th>Year</th>
<th>Comparison</th>
<th>Last BMD, year</th>
<th>Sample: Drug</th>
<th>Sample: Control</th>
<th>DRUG: %Change: Mean</th>
<th>CONTROL: %Change: Mean</th>
<th>DRUG: LS BMD, SD</th>
<th>CONTROL: LS BMD, SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Liberman</td>
<td>1995</td>
<td>alendronate (10mg/day[d]) vs. placebo</td>
<td>3</td>
<td>526</td>
<td>355</td>
<td>8.00</td>
<td>-0.80</td>
<td>4.30</td>
<td>2.36</td>
</tr>
<tr>
<td>2</td>
<td>Montessori</td>
<td>1997</td>
<td>cyclyc etidronate (400mg/d) vs. calcium(500mg/d)</td>
<td>2</td>
<td>40</td>
<td>40</td>
<td>6.28</td>
<td>-0.03</td>
<td>5.02</td>
<td>10.00</td>
</tr>
<tr>
<td>3</td>
<td>Meunier</td>
<td>1997</td>
<td>cyclyc etidronate (400mg/d) vs. placebo</td>
<td>2</td>
<td>27</td>
<td>27</td>
<td>0.58</td>
<td>-2.34</td>
<td>5.20</td>
<td>4.18</td>
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<td>4</td>
<td>Mortensen</td>
<td>1998</td>
<td>risedronate(5mg/d) vs. placebo</td>
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<td>17</td>
<td>20</td>
<td>-2.30</td>
<td>-5.60</td>
<td>3.30</td>
<td>4.47</td>
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<td>Harris</td>
<td>1999</td>
<td>risedronate(5mg/d) vs. placebo</td>
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<td>489</td>
<td>450</td>
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<td>Cummings</td>
<td>1998</td>
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<td>2218</td>
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<td>1.50</td>
<td>7.84</td>
<td>6.28</td>
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<tr>
<td>7</td>
<td>Pols</td>
<td>1999</td>
<td>alendronate (10mg/d) vs. placebo</td>
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<td>950</td>
<td>958</td>
<td>5.00</td>
<td>0.10</td>
<td>3.20</td>
<td>3.40</td>
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<td>Register</td>
<td>2000</td>
<td>risedronate(5mg/d) vs. placebo</td>
<td>3</td>
<td>407</td>
<td>407</td>
<td>6.86</td>
<td>1.21</td>
<td>11.53</td>
<td>10.091</td>
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<td>Brumsen</td>
<td>2002</td>
<td>pamidronate (150mg/day) vs. placebo</td>
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<td>46</td>
<td>45</td>
<td>9.02</td>
<td>3.70</td>
<td>9.09</td>
<td>6.24</td>
</tr>
<tr>
<td>10</td>
<td>Reid IR</td>
<td>2002</td>
<td>zolendronic acid (4x0.25mg) vs. placebo</td>
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<td>60</td>
<td>59</td>
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<td>0.02</td>
<td>2.32</td>
<td>3.07</td>
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<tr>
<td>11</td>
<td>McCloskey</td>
<td>2004</td>
<td>clodronate(800mg/d) vs. placebo</td>
<td>3</td>
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<tr>
<td>12</td>
<td>Bone</td>
<td>2004</td>
<td>alendronate (10mg/d) vs. placebo</td>
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<td>86</td>
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<td>5.20</td>
<td>5.35</td>
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<tr>
<td>13</td>
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<td>2006</td>
<td>alendronate (10mg/d) vs. placebo</td>
<td>5</td>
<td>662</td>
<td>437</td>
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<td>1.52</td>
<td>6.18</td>
<td>6.06</td>
</tr>
<tr>
<td>14</td>
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<td>2007</td>
<td>zolendronic acid (5mg) vs. placebo</td>
<td>3</td>
<td>3889</td>
<td>3876</td>
<td>6.71</td>
<td>0.00</td>
<td>6.20</td>
<td>6.20</td>
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N denotes study number, BMD denotes bone mineral density; SD denotes standard deviation.
<table>
<thead>
<tr>
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<th>First Author</th>
<th>Year</th>
<th>Comparison</th>
<th>Last BMD, year</th>
<th>Sample: Drug</th>
<th>Sample: Control</th>
<th>DRUG: FN BMD, %Change: Mean</th>
<th>CONTROL: FN BMD, %Change: Mean</th>
<th>DRUG: FN BMD, %Change: SD</th>
<th>CONTROL: FN BMD, %Change: SD</th>
</tr>
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<tbody>
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<td>1995</td>
<td>alendronate (10mg/d) vs. placebo</td>
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<td>1997</td>
<td>cyclyc etidronate (400mg/d) vs. calcium(500mg/d)</td>
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<td>Meunier</td>
<td>1997</td>
<td>cyclyc etidronate (400mg/d) vs. placebo</td>
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<td>pamidronate (150mg/day) vs. placebo</td>
<td>3</td>
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<td>6.30</td>
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N denotes study number, BMD denotes bone mineral density; SD denotes standard deviation.
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<th>Last FU (yrs)</th>
<th>Sample: Drug</th>
<th>Sample: Control</th>
<th>Drug: All reported fractures</th>
<th>Control: All reported fractures</th>
<th>Drug: All clinical fractures</th>
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<th>Drug: VF</th>
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<td>Liberman</td>
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<td>355</td>
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<tr>
<td>2</td>
<td>Montessori</td>
<td>1997</td>
<td>Cyclyc Etidronate (400mg/d) vs. calcium(500mg/d)</td>
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<tr>
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<td>Meunier</td>
<td>1997</td>
<td>Cyclyc Etidronate (400mg/d) vs. placebo</td>
<td>2</td>
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<td>NA</td>
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<tr>
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<td>McCloskey</td>
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<td>Clodronate(800mg/d) vs. placebo</td>
<td>3</td>
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<td>301</td>
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<td>NA</td>
<td>33</td>
<td>63</td>
<td>NA</td>
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<tr>
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<td>Alendronate (10mg/d) vs. placebo</td>
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<td>5</td>
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<td>NA</td>
<td>4</td>
<td>5</td>
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<tr>
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<td>Black</td>
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<td>132</td>
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<td>60</td>
<td>46</td>
<td>125</td>
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<tr>
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<td>Zolendronic (5mg) vs. placebo</td>
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<td>3861</td>
<td>400</td>
<td>766</td>
<td>308</td>
<td>456</td>
<td>92</td>
<td>310</td>
<td>292</td>
</tr>
</tbody>
</table>

N denotes study number, FU denotes follow-up; VF denotes vertebral fractures and nonVF denotes non-vertebral fractures.
Table A4.3. Additional results: BRMAs with complete data on BMD and fractures – bisphosphonates and vitamin D3 and calcium (WinBUGs outputs)

1a. Bisphosphonates trials – estimation of the between-study correlation (lumbar spine BMD and all fractures), assuming within-study correlation -0.25

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mean</th>
<th>standard deviation (sd)</th>
<th>Monte Carlo error (MC error)</th>
<th>2.5%</th>
<th>median</th>
<th>97.5%</th>
<th>start</th>
<th>sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population odds ratio (OR)</td>
<td>0.5652</td>
<td>0.05442</td>
<td>5.105E-4</td>
<td>0.4616</td>
<td>0.5637</td>
<td>0.6771</td>
<td>10000</td>
<td>91001</td>
</tr>
<tr>
<td>Between-study correlation</td>
<td>-0.02091</td>
<td>0.4865</td>
<td>0.005098</td>
<td>-0.8383</td>
<td>-0.02739</td>
<td>0.8173</td>
<td>10000</td>
<td>91001</td>
</tr>
<tr>
<td>Future OR</td>
<td>0.5796</td>
<td>0.1482</td>
<td>6.888E-4</td>
<td>0.338</td>
<td>0.5637</td>
<td>0.9198</td>
<td>10000</td>
<td>91001</td>
</tr>
<tr>
<td>phi[1] – log-odds ratio</td>
<td>-0.5753</td>
<td>0.09667</td>
<td>9.128E-4</td>
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<td>-0.5732</td>
<td>-0.3899</td>
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<td>91001</td>
</tr>
<tr>
<td>phi[2] – future mean difference - MD (BMD at the lumbar spine), %</td>
<td>5.308</td>
<td>1.312</td>
<td>0.04863</td>
<td>2.721</td>
<td>5.316</td>
<td>7.969</td>
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<td>91001</td>
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<tr>
<td>phi_new[1] – future log-odds ratio</td>
<td>-0.5762</td>
<td>0.2482</td>
<td>0.001191</td>
<td>-1.085</td>
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<td>-0.0836</td>
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</tr>
<tr>
<td>phi_new[2] – future MD (BMD at the lumbar spine), %</td>
<td>5.305</td>
<td>1.49</td>
<td>0.0488</td>
<td>2.383</td>
<td>5.313</td>
<td>8.266</td>
<td>10000</td>
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</tr>
<tr>
<td>tau[1,1] – precision, variance (fractures)</td>
<td>37.39</td>
<td>21.84</td>
<td>0.1533</td>
<td>9.846</td>
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<td>92.42</td>
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<tr>
<td>tau[1,2] – precision, covariance</td>
<td>0.2613</td>
<td>8.265</td>
<td>0.07966</td>
<td>-16.84</td>
<td>0.267</td>
<td>17.32</td>
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<td>91001</td>
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<tr>
<td>tau[2,1] – precision, covariance</td>
<td>0.2613</td>
<td>8.265</td>
<td>0.07966</td>
<td>-16.84</td>
<td>0.267</td>
<td>17.32</td>
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</tr>
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<td>tau[2,2] – precision, between-study variance (BMD)</td>
<td>6.333</td>
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<td>0.6943</td>
<td>5.115</td>
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<tr>
<td>v0[1,1] - variance (fractures)</td>
<td>0.05192</td>
<td>0.03501</td>
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<tr>
<td>v0[1,2] - covariance</td>
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<td>0.1077</td>
<td>0.001094</td>
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<td>-0.002116</td>
<td>0.1997</td>
<td>10000</td>
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<td>-0.005347</td>
<td>0.1077</td>
<td>0.001094</td>
<td>-0.2303</td>
<td>-0.002116</td>
<td>0.1997</td>
<td>10000</td>
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<td>v0[2,2] - between-study variance (BMD)</td>
<td>0.4929</td>
<td>0.7736</td>
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<td>0.2744</td>
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</table>

Posterior distribution for the between-study correlation: bisphosphonates trials, within-study correlation = -0.25
1b. Bisphosphonates trials – estimation of the between-study correlation, assuming the within-study correlation of -0.175 (calculated from the trial data)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mean</th>
<th>sd</th>
<th>MC error</th>
<th>2.5%</th>
<th>median</th>
<th>97.5%</th>
<th>start</th>
<th>sample</th>
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</thead>
<tbody>
<tr>
<td>Population odds ratio (OR)</td>
<td>0.5654</td>
<td>0.05453</td>
<td>4.837E-4</td>
<td>0.4617</td>
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<tr>
<td>Between-study correlation</td>
<td>-0.01638</td>
<td>0.4865</td>
<td>0.005092</td>
<td>-0.8362</td>
<td>-0.02183</td>
<td>0.8203</td>
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</tr>
<tr>
<td>Future OR</td>
<td>0.5799</td>
<td>0.1483</td>
<td>6.684E-4</td>
<td>0.3385</td>
<td>0.564</td>
<td>0.92</td>
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<td>phi[1] – log-odds ratio</td>
<td>-0.5749</td>
<td>0.0968</td>
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<td>-0.5728</td>
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<tr>
<td>phi[2] – future mean difference - MD (BMD at the lumbar spine), %</td>
<td>5.344</td>
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<td>0.04927</td>
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<td>phi_new[1] – future log-odds ratio</td>
<td>-0.5758</td>
<td>0.2483</td>
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<td>phi_new[2] – future MD (BMD at the lumbar spine), %</td>
<td>5.341</td>
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<td>tau[1,1] – precision, variance (fractures)</td>
<td>37.45</td>
<td>21.93</td>
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<td>32.52</td>
<td>92.89</td>
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<tr>
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<td>0.07959</td>
<td>-16.93</td>
<td>0.2094</td>
<td>17.27</td>
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<td>tau[2,2] – precision, between-study variance (BMD)</td>
<td>6.329</td>
<td>4.874</td>
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<td>0.1078</td>
<td>0.00111</td>
<td>-0.2272</td>
<td>-0.001778</td>
<td>0.2034</td>
<td>10000</td>
<td>92001</td>
</tr>
<tr>
<td>v0[2,1] - covariance</td>
<td>-0.004268</td>
<td>0.1078</td>
<td>0.00111</td>
<td>-0.2272</td>
<td>-0.001778</td>
<td>0.2034</td>
<td>10000</td>
<td>92001</td>
</tr>
<tr>
<td>v0[2,2] - between-study variance (BMD)</td>
<td>0.4933</td>
<td>0.7738</td>
<td>0.00893</td>
<td>0.06431</td>
<td>0.2745</td>
<td>2.279</td>
<td>10000</td>
<td>92001</td>
</tr>
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</table>

Posterior distribution for the between-study correlation: bisphosphonates trials, within-study correlation = -0.175
# 2. Vitamin D trials – estimation of the between-study correlation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>mean</th>
<th>sd</th>
<th>MC error</th>
<th>2.5%</th>
<th>median</th>
<th>97.5%</th>
<th>start</th>
<th>sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population OR</td>
<td>0.6565</td>
<td>34.59</td>
<td>0.1355</td>
<td>0.0312</td>
<td>0.2473</td>
<td>1.787</td>
<td>20000</td>
<td>243003</td>
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<tr>
<td><strong>Between-study correlation</strong></td>
<td>0.5587</td>
<td>0.617</td>
<td><strong>0.007849</strong></td>
<td><strong>-0.9494</strong></td>
<td><strong>0.8868</strong></td>
<td><strong>0.9951</strong></td>
<td><strong>20000</strong></td>
<td><strong>243003</strong></td>
</tr>
<tr>
<td>phi[1] – log-odds ratio</td>
<td>-1.413</td>
<td>1.003</td>
<td>0.009546</td>
<td>-3.467</td>
<td>-1.397</td>
<td>0.5804</td>
<td>20000</td>
<td>243003</td>
</tr>
<tr>
<td>phi[2] – future MD (FN BMD), %</td>
<td>1.378</td>
<td>1.59</td>
<td>0.02408</td>
<td>-1.64</td>
<td>1.348</td>
<td>4.58</td>
<td>20000</td>
<td>243003</td>
</tr>
<tr>
<td>tau[1,1] – between-study variance (fractures)</td>
<td>3.076</td>
<td>5.252</td>
<td>0.02797</td>
<td>0.537</td>
<td>1.855</td>
<td>12.94</td>
<td>20000</td>
<td>243003</td>
</tr>
<tr>
<td>tau[1,2] – covariance</td>
<td>1.955</td>
<td>5.201</td>
<td>0.04904</td>
<td>-2.146</td>
<td>1.037</td>
<td>11.57</td>
<td>20000</td>
<td>243003</td>
</tr>
<tr>
<td>tau[2,1] – covariance</td>
<td>1.955</td>
<td>5.201</td>
<td>0.04904</td>
<td>-2.146</td>
<td>1.037</td>
<td>11.57</td>
<td>20000</td>
<td>243003</td>
</tr>
<tr>
<td>tau[2,2] – between-study variance (BMD)</td>
<td>3.212</td>
<td>8.145</td>
<td>0.07691</td>
<td>0.0981</td>
<td>1.175</td>
<td>18.38</td>
<td>20000</td>
<td>243003</td>
</tr>
</tbody>
</table>

**Posterior distribution for the between-study correlation: vitamin D trials**
Table A4.4a. Sensitivity of the vitamin K2 BRMA models to clinically plausible values of the within-study correlations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LS BMD &amp; all fractures (reference)</th>
<th>LS BMD &amp; all fracture</th>
<th>LS BMD &amp; all fractures</th>
<th>FN BMD &amp; nonVF (reference)</th>
<th>FN BMD &amp; nonVF</th>
<th>FN BMD &amp; nonVF</th>
<th>VF &amp; nonVF (reference)</th>
<th>VF &amp; nonVF</th>
<th>VF &amp; nonVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within-study correlation - $\rho_{wi}$</td>
<td>-0.25</td>
<td>-0.1</td>
<td>-0.01</td>
<td>-0.25</td>
<td>-0.1</td>
<td>-0.01</td>
<td>-0.1</td>
<td>0.80</td>
<td>0.90</td>
</tr>
<tr>
<td>Pooled mean difference (MD) / Population odds ratio (OR)</td>
<td>1.1 (0.1,2.1)</td>
<td>1.1 (0.1,2.1)</td>
<td>1.1 (0.2,2.2)</td>
<td>0.1 (-0.8,1.1)</td>
<td>0.1 (-0.9,1.1)</td>
<td>0.1 (-0.9,1.1)</td>
<td>0.8 (0.5,1.1)</td>
<td>0.8 (0.5,1.1)</td>
<td>0.8 (0.5,1.1)</td>
</tr>
<tr>
<td>Future MD / Future OR $\dagger$ , mean (95%CrI)</td>
<td>1.1 (-1.4,3.6)</td>
<td>1.1 (-1.4,3.8)</td>
<td>1.1 (-1.4,3.8)</td>
<td>0.1 (-1.4,1.7)</td>
<td>0.1 (-1.4,1.7)</td>
<td>0.1 (-1.4,1.7)</td>
<td>0.8 (0.4,1.5)</td>
<td>0.8 (0.4,1.5)</td>
<td>0.9 (0.4,1.5)</td>
</tr>
<tr>
<td>Population OR , mean (95%CrI)</td>
<td>0.7 (0.5,1.0)</td>
<td>0.7 (0.5,1.0)</td>
<td>0.7 (0.5,1.0)</td>
<td>0.9 (0.5,1.3)</td>
<td>0.9 (0.5,1.3)</td>
<td>0.9 (0.5,1.3)</td>
<td>0.7 (0.3,1.4)</td>
<td>0.8 (0.3,1.4)</td>
<td>0.7 (0.3,1.4)</td>
</tr>
<tr>
<td>Future OR , mean (95%CrI)</td>
<td>0.8 (0.4,1.4)</td>
<td>0.8 (0.4,1.4)</td>
<td>0.8 (0.3,1.4)</td>
<td>0.9 (0.4,1.6)</td>
<td>0.9 (0.4,1.5)</td>
<td>0.9 (0.4,1.6)</td>
<td>0.9 (0.2,2.5)</td>
<td>0.9 (0.2,2.5)</td>
<td>0.9 (0.1,2.6)</td>
</tr>
<tr>
<td>Probability of benefit in both outcomes, current trials:</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>P(any benefit), %</td>
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<td>95</td>
<td>95</td>
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<td>49</td>
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<tr>
<td>P(clinically important benefit), %</td>
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<td>62</td>
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<tr>
<td>Probability of benefit in both outcomes, future trials:</td>
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<td></td>
</tr>
<tr>
<td>P(any benefit), %</td>
<td>71</td>
<td>72</td>
<td>72</td>
<td>43</td>
<td>43</td>
<td>42</td>
<td>61</td>
<td>62</td>
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</tr>
<tr>
<td>P(clinically important benefit), %</td>
<td>45</td>
<td>45</td>
<td>46</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>35</td>
<td>36</td>
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<tr>
<td>Between-study correlation – $\rho_b$ Mean (95%CrI)</td>
<td>-0.2 (-0.9,0.9)</td>
<td>-0.2 (-0.9,0.9)</td>
<td>-0.2 (-0.9,0.9)</td>
<td>-0.02 (-0.8,0.8)</td>
<td>-0.01 (-0.8,0.8)</td>
<td>-0.01 (-0.8,0.8)</td>
<td>0.2 (-0.7,0.9)</td>
<td>0.2 (-0.7,0.9)</td>
<td>0.2 (-0.7,0.9)</td>
</tr>
</tbody>
</table>

BMD denotes bone mineral density; LS denotes lumbar spine, FN denotes femoral neck, VF denotes vertebral fractures, non VF denotes non-vertebral fractures $\dagger$ OR for vertebral fractures.
Table A4.4b. Sensitivity of the vitamin K1 BRMA models to clinically plausible values of the within-study correlations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LS BMD &amp; all fractures (reference)</th>
<th>LS BMD &amp; all fracture</th>
<th>LS BMD &amp; all fractures</th>
<th>FN BMD &amp; nonVF (reference)</th>
<th>FN BMD &amp; nonVF</th>
<th>FN BMD &amp; nonVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within-study correlation - $\rho_{w[i]}$</td>
<td>-0.25</td>
<td>-0.1</td>
<td>-0.01</td>
<td>-0.25</td>
<td>-0.1</td>
<td>-0.01</td>
</tr>
<tr>
<td>Pooled mean difference (MD) / Population odds ratio (OR) $^J$, mean (95%CrI)</td>
<td>-0.2 (-0.9, 0.6)</td>
<td>-0.2 (-0.9, 0.6)</td>
<td>-0.2 (-0.9, 0.6)</td>
<td>0.6 (-0.2, 1.5)</td>
<td>0.6 (-0.2, 1.5)</td>
<td>0.6 (-0.3, 1.5)</td>
</tr>
<tr>
<td>Future MD / Future OR $^J$, mean (95%CrI)</td>
<td>-0.2 (-1.5, 1.2)</td>
<td>-0.2 (-1.5, 1.2)</td>
<td>-0.2 (-1.5, 1.2)</td>
<td>0.6 (-0.9, 2.2)</td>
<td>0.6 (-0.9, 2.2)</td>
<td>0.6 (-0.9, 2.2)</td>
</tr>
<tr>
<td>Population OR, mean (95%CrI)</td>
<td>0.9 (0.5, 1.6)</td>
<td>0.8 (0.4, 1.6)</td>
<td>0.9 (0.5, 1.6)</td>
<td>0.5 (0.2, 1.2)</td>
<td>0.5 (0.2, 1.2)</td>
<td>0.5 (0.2, 1.2)</td>
</tr>
<tr>
<td>Future OR, mean (95%CrI)</td>
<td>0.9 (0.4, 1.9)</td>
<td>0.9 (0.4, 1.8)</td>
<td>0.9 (0.4, 1.8)</td>
<td>0.6 (0.2, 1.3)</td>
<td>0.6 (0.2, 1.3)</td>
<td>0.6 (0.2, 1.3)</td>
</tr>
<tr>
<td>Probability of benefit in both outcomes, current trials:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>P(any benefit), %</td>
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<td>22</td>
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<td>87</td>
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<td>P(clinically important benefit), %</td>
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<tr>
<td>Probability of benefit in both outcomes, future trials:</td>
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<td></td>
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<tr>
<td>P(any benefit), %</td>
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<td>26</td>
<td>26</td>
<td>75</td>
<td>74</td>
<td>74</td>
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<tr>
<td>P(clinically important benefit), %</td>
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<td>6</td>
<td>6</td>
<td>46</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Between-study correlation – $\rho_{b}$</td>
<td>-0.01 (-0.8, 0.8)</td>
<td>-0.004 (-0.8, 0.8)</td>
<td>-0.01 (-0.8, 0.8)</td>
<td>-0.02 (-0.8, 0.8)</td>
<td>-0.02 (-0.8, 0.8)</td>
<td>-0.01 (-0.8, 0.8)</td>
</tr>
<tr>
<td>Mean (95%CrI)</td>
<td>-0.01 (-0.8, 0.8)</td>
<td>-0.01 (-0.8, 0.8)</td>
<td>-0.01 (-0.8, 0.8)</td>
<td>-0.02 (-0.8, 0.8)</td>
<td>-0.02 (-0.8, 0.8)</td>
<td>-0.01 (-0.8, 0.8)</td>
</tr>
</tbody>
</table>

BMD denotes bone mineral density; LS denotes lumbar spine, FN denotes femoral neck, nonVF denotes non-vertebral fractures.
Table A4.4c. Sensitivity of the vitamin K2 BRMA models to the extreme values of the within-study correlations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LS BMD &amp; all fractures (reference)</th>
<th>LS BMD &amp; all fractures</th>
<th>LS BMD &amp; all fractures</th>
<th>FN BMD &amp; nonVF (reference)</th>
<th>FN BMD &amp; nonVF</th>
<th>FN BMD &amp; nonVF</th>
<th>VF &amp; nonVF (reference)</th>
<th>VF &amp; nonVF</th>
<th>VF &amp; nonVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within-study correlation - ρₜ[i]</td>
<td>-0.25</td>
<td>-0.90</td>
<td>+0.90</td>
<td>-0.25</td>
<td>-0.90</td>
<td>+0.90</td>
<td>0.80</td>
<td>-0.10</td>
<td>-0.90</td>
</tr>
<tr>
<td>Pooled mean difference (MD) / Population odds ratio (OR) †, mean (95%CrI)</td>
<td>1.1 (0.1,2.1)</td>
<td>0.8 (-0.1,1.8)</td>
<td>1.3 (0.3,2.4)</td>
<td>0.1 (-0.8,1.1)</td>
<td>0.1 (-0.8,1.1)</td>
<td>0.1 (-0.9,1.1)</td>
<td>0.8 (0.5,1.1) †</td>
<td>0.8 (0.5,1.1) †</td>
<td>0.6 (0.4,1.0) †</td>
</tr>
<tr>
<td>Future MD / Future OR †, mean (95%CrI)</td>
<td>1.1 (-1.4,3.6)</td>
<td>0.8 (-1.7,3.4)</td>
<td>1.3 (-1.4,4.1)</td>
<td>0.1 (-1.4,1.7)</td>
<td>0.1 (-1.4,1.6)</td>
<td>0.1 (-1.4,1.7)</td>
<td>0.8 (0.4,1.5) †</td>
<td>0.8 (0.3,1.6) †</td>
<td>0.7 (0.2,1.8) †</td>
</tr>
<tr>
<td>Population OR, mean (95%CrI)</td>
<td>0.7 (0.5,1.0)</td>
<td>0.7 (0.5,1.0)</td>
<td>0.7 (0.4,1.0)</td>
<td>0.9 (0.5,1.3)</td>
<td>0.8 (0.5,1.3)</td>
<td>0.8 (0.5,1.3)</td>
<td>0.7 (0.3,1.4)</td>
<td>0.6 (0.2,1.3)</td>
<td>0.5 (0.1,1.0)</td>
</tr>
<tr>
<td>Future OR, mean (95%CrI)</td>
<td>0.8 (0.4,1.4)</td>
<td>0.7 (0.3,1.3)</td>
<td>0.7 (0.3,1.4)</td>
<td>0.9 (0.4,1.5)</td>
<td>0.9 (0.4,1.5)</td>
<td>0.9 (0.4,1.6)</td>
<td>0.9 (0.2,2.5)</td>
<td>0.9 (0.1,2.6)</td>
<td>1.9 (0.0,2.9)</td>
</tr>
<tr>
<td>Probability of benefit in both outcomes, current trials:</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(any benefit), %</td>
<td>95</td>
<td>95</td>
<td>97</td>
<td>49</td>
<td>49</td>
<td>49</td>
<td>80</td>
<td>85</td>
<td>95</td>
</tr>
<tr>
<td>P(clinically important benefit), %</td>
<td>62</td>
<td>63</td>
<td>77</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>40</td>
<td>49</td>
<td>80</td>
</tr>
<tr>
<td>Probability of benefit in both outcomes, future trials:</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>P(any benefit), %</td>
<td>71</td>
<td>70</td>
<td>77</td>
<td>43</td>
<td>43</td>
<td>42</td>
<td>61</td>
<td>65</td>
<td>76</td>
</tr>
<tr>
<td>P(clinically important benefit), %</td>
<td>45</td>
<td>46</td>
<td>57</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>35</td>
<td>35</td>
<td>42</td>
</tr>
<tr>
<td>Between-study correlation – ρ_b</td>
<td>-0.2/-0.4</td>
<td>-0.3/-0.5</td>
<td>-0.5/-0.7</td>
<td>-0.01/-0.02</td>
<td>-0.01/-0.01</td>
<td>-0.02/-0.03</td>
<td>0.2/0.3</td>
<td>0.3/0.5</td>
<td>0.7/0.8</td>
</tr>
<tr>
<td>Mean/Median (95%CrI)</td>
<td>(-0.9,0.9)</td>
<td>(-0.9,0.9)</td>
<td>(-0.9,0.9)</td>
<td>(-0.8,0.8)</td>
<td>(-0.8,0.8)</td>
<td>(-0.7,0.9)</td>
<td>(-0.7,0.9)</td>
<td>(-0.2,1.0)</td>
<td>(-0.2,1.0)</td>
</tr>
</tbody>
</table>

BMD denotes bone mineral density; LS denotes lumbar spine, FN denotes femoral neck, VF denotes vertebral fractures, non VF denotes non-vertebral fractures; OR for vertebral fractures.
Table A4.4d. Sensitivity of the vitamin K1 BRMA models to the extreme values of the within-study correlations

<table>
<thead>
<tr>
<th>Parameters</th>
<th>LS BMD &amp; all fractures (reference)</th>
<th>LS BMD &amp; all fractures</th>
<th>LS BMD &amp; all fractures</th>
<th>FN BMD &amp; nonVF (reference)</th>
<th>FN BMD &amp; nonVF</th>
<th>FN BMD &amp; nonVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within-study correlation - ρ_w[i]</td>
<td>-0.25</td>
<td>-0.90</td>
<td>+0.90</td>
<td>-0.25</td>
<td>-0.90</td>
<td>+0.90</td>
</tr>
<tr>
<td>Pooled mean difference (MD) / Population odds ratio (OR) [^1], mean (95%CrI)</td>
<td>-0.2 (-0.9, 0.6)</td>
<td>-0.2 (-0.9, 0.6)</td>
<td>-0.2 (-0.9, 0.6)</td>
<td>0.6 (-0.2, 1.5)</td>
<td>0.6 (-0.2, 1.5)</td>
<td>0.6 (-0.3, 1.5)</td>
</tr>
<tr>
<td>Future MD / Future OR [^1], mean (95%CrI)</td>
<td>-0.2 (-1.5, 1.2)</td>
<td>-0.2 (-1.5, 1.2)</td>
<td>-0.2 (-1.5, 1.2)</td>
<td>0.6 (-0.9, 2.2)</td>
<td>0.6 (-0.9, 2.2)</td>
<td>0.6 (-0.9, 2.2)</td>
</tr>
<tr>
<td>Population OR, mean (95%CrI)</td>
<td>0.9 (0.5, 1.6)</td>
<td>0.9 (0.5, 1.6)</td>
<td>0.9 (0.4, 1.5)</td>
<td>0.5 (0.2, 1.2)</td>
<td>0.5 (0.2, 1.1)</td>
<td>0.6 (0.2, 1.2)</td>
</tr>
<tr>
<td>Future OR, mean (95%CrI)</td>
<td>0.9 (0.4, 1.9)</td>
<td>0.9 (0.4, 1.8)</td>
<td>0.9 (0.4, 1.8)</td>
<td>0.6 (0.2, 1.3)</td>
<td>0.5 (0.2, 1.2)</td>
<td>0.6 (0.2, 1.4)</td>
</tr>
<tr>
<td>Probability of benefit in both outcomes, current trials:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P(any benefit), %</td>
<td>22</td>
<td>24</td>
<td>20</td>
<td>87</td>
<td>89</td>
<td>86</td>
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<tr>
<td>Pclinically important benefit), %</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>49</td>
<td>52</td>
<td>44</td>
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<tr>
<td>Probability of benefit in both outcomes, future trials:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>P(any benefit), %</td>
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<td>24</td>
<td>75</td>
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<tr>
<td>Pclinically important benefit), %</td>
<td>6</td>
<td>7</td>
<td>5</td>
<td>46</td>
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<tr>
<td>Between-study correlation – ρ_b</td>
<td>-0.01/-0.01</td>
<td>-0.06/-0.06</td>
<td>-0.01/+0.02</td>
<td>-0.02/-0.03</td>
<td>-0.07/-0.10</td>
<td>+0.02/+0.02</td>
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<tr>
<td>Mean/Median (95%CrI)</td>
<td>(-0.8, 0.8)</td>
<td>(-0.8, 0.8)</td>
<td>(-0.8, 0.8)</td>
<td>(-0.8, 0.8)</td>
<td>(-0.8, 0.8)</td>
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BMD denotes bone mineral density; LS denotes lumbar spine, FN denotes femoral neck, nonVF denotes non-vertebral fractures.
Table A4.5. Original and additional model parameters: Bayesian URMA and BRMA.

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<tr>
<th>Model Parameters</th>
<th>Base Case Values (95% CI/SE)</th>
<th>Source</th>
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<td><strong>RISKS</strong></td>
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<td>Subsequent fracture following</td>
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<tr>
<td>hip fracture</td>
<td>2.40 (1.90-3.20)</td>
<td>(161)</td>
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<tr>
<td>vertebral clinical/morphometric fracture</td>
<td>2.00 (1.70-2.40)</td>
<td>(161)</td>
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<tr>
<td>wrist fracture</td>
<td>1.90 (1.70-2.30)</td>
<td>(161)</td>
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<tr>
<td>Death, 1st year following a hip fracture</td>
<td>1.37 (1.10-1.50)</td>
<td>(5)</td>
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<tr>
<td>Fracture risk with alendronate (70 mg/week)</td>
<td></td>
<td></td>
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<tr>
<td>hip fracture</td>
<td>0.62 (0.40-0.98)</td>
<td>(175)</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.56 (0.46-0.68)</td>
<td>(175)</td>
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<tr>
<td>wrist fracture</td>
<td>0.64 (0.30-1.35)</td>
<td>(175)</td>
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<tr>
<td>Fracture risk with vitamin D3 plus calcium</td>
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<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.68 (0.50-0.92)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.87 (0.65-1.14)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.69 (0.18-2.54)</td>
<td>Meta-analysis</td>
</tr>
<tr>
<td>Fracture risk with vitamin K2 (45 mg/day) – original</td>
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<td></td>
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<tr>
<td>hip fracture</td>
<td>0.30 (0.05-1.74)</td>
<td>(56)</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.40 (0.25-0.65)</td>
<td>(56)</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.54 (0.20-0.85)</td>
<td>(168)</td>
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<td>Fracture risk with vitamin K2 (45 mg/day) - URMA†/ URMA§</td>
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<tr>
<td>hip fracture - non-vertebral fractures</td>
<td>0.47 (0.1-1.3)†/ 1.0 (0.0-5.5)§</td>
<td>Bayesian URMA</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.67 (0.2-1.5)†/ 1.2 (0.1-5.2)§</td>
<td>Bayesian URMA</td>
</tr>
<tr>
<td>wrist fracture - non-vertebral fractures</td>
<td>0.47 (0.1-1.3)†/ 1.0 (0.0-5.5)§</td>
<td>Bayesian URMA</td>
</tr>
<tr>
<td>Fracture risk with vitamin K2 (45 mg/day) - BRMA†/ BRMA§</td>
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<tr>
<td>hip fracture - non-vertebral fractures and FN BMD</td>
<td>0.85 (0.5-1.3)†/ 0.87 (0.4-1.6)§</td>
<td>Bayesian BRMA</td>
</tr>
<tr>
<td>vertebral fracture and LS BMD</td>
<td>0.81 (0.5-1.1)†/ 0.84 (0.4-1.5)§</td>
<td>Bayesian BRMA</td>
</tr>
<tr>
<td>wrist fracture - non-vertebral fractures and FN BMD</td>
<td>0.85 (0.5-1.3)†/ 0.87 (0.4-1.6)§</td>
<td>Bayesian BRMA</td>
</tr>
<tr>
<td>Fracture risk with vitamin K1 (5 mg/day) -original</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture</td>
<td>0.34 (0.01-8.42)</td>
<td>ECKO, (60)</td>
</tr>
<tr>
<td>vertebral fracture</td>
<td>0.45 (0.14-1.47)</td>
<td>ECKO</td>
</tr>
<tr>
<td>wrist fracture</td>
<td>0.33 (0.09-1.25)</td>
<td>ECKO</td>
</tr>
<tr>
<td>Fracture risk with vitamin K1 (5 mg/day) -BRMA†/ BRMA§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip fracture - non-vertebral fractures and FN BMD</td>
<td>0.54 (0.2-1.2)†/ 0.56 (0.2-1.3)§</td>
<td>Bayesian BRMA</td>
</tr>
<tr>
<td>vertebral fracture and LS BMD</td>
<td>0.59 (0.1-1.8)†/ 0.61 (0.1-1.9)§</td>
<td>Bayesian BRMA</td>
</tr>
<tr>
<td>wrist fracture - non-vertebral fractures and FN BMD</td>
<td>0.54 (0.2-1.2)†/ 0.56 (0.2-1.3)§</td>
<td>Bayesian BRMA</td>
</tr>
<tr>
<td><strong>UTILITIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture, first year</td>
<td>0.890 (0.043)</td>
<td>(178)</td>
</tr>
<tr>
<td>Hip fracture, subsequent years</td>
<td>0.925 (0.048)</td>
<td>(175)</td>
</tr>
<tr>
<td>Clinical vertebral fracture, first year</td>
<td>0.900 (0.031)</td>
<td>(178)</td>
</tr>
<tr>
<td>Clinical vertebral fracture, subsequent years</td>
<td>0.930 (0.008)</td>
<td>(175)</td>
</tr>
<tr>
<td>Wrist fracture, first year</td>
<td>0.980 (0.005)</td>
<td>(175)</td>
</tr>
<tr>
<td>No fracture, age 50</td>
<td>0.985 (0.010)</td>
<td>(181)</td>
</tr>
<tr>
<td><strong>COSTS (USD)‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture, first year</td>
<td>51139.20</td>
<td>(11)</td>
</tr>
<tr>
<td>Hip fracture, 2-5 years</td>
<td>3639.90</td>
<td>(11)</td>
</tr>
<tr>
<td>Clinical vertebral fracture, first year</td>
<td>1659.40</td>
<td>(11)</td>
</tr>
<tr>
<td>Clinical vertebral fracture, 2-5 years</td>
<td>371.90</td>
<td>(11)</td>
</tr>
<tr>
<td>Wrist fracture</td>
<td>1030.30</td>
<td>(11)</td>
</tr>
<tr>
<td>Alendronate, 70 mg/week (generic)</td>
<td>131.04</td>
<td>(158)</td>
</tr>
<tr>
<td>Vitamin K2, 45 mg/day</td>
<td>865.20</td>
<td>(185)</td>
</tr>
<tr>
<td>Vitamin K1, 5 mg/day</td>
<td>199.80</td>
<td>(183)</td>
</tr>
<tr>
<td>Vitamin D3 with calcium, 800 IU + 1200 mg/day</td>
<td>89.90</td>
<td>(158)</td>
</tr>
</tbody>
</table>

URMA denotes univariate random-effects meta-analysis; BRMA denotes bivariate random-effects meta-analysis; † Bayesian posterior population odds ratios (ORs) – current studies; § Bayesian posterior predictive ORs
9.2 Appendix 2: Figures
Figure A4.1. Cost-effectiveness acceptability curves (CEAC) for the vitamin K2 strategy vs. the vitamin D and calcium strategy: Published, URMA-derived and BRMA-derived ORs for the efficacy of vitamin K2.
Figure A4.2. Cost-effectiveness acceptability curve (CEAC) for the vitamin K1 strategy vs. the vitamin D and calcium strategy: Published and BRMA-derived ORs for the efficacy of vitamin K1.
EXAMPLE BRMA MODEL - VITAMIN K2: lumbar spine BMD and all fractures

model

### 1st PART : VITAMIN K studies
# i indexes study number, N1 denotes number of trials with complete data, N denotes a total number of combined trials in BRMA

for(i in (N1+1):N)[

# binary outcome: fractures
# This part of the model generates rt_bin and rc_bin when they are missing
# They are sampled from these distributions, which depend on the sample sizes
# and pt and pc
# pc is sampled from an informative prior
# logit(pt) is equal to logit(pc) + mu[i,1]
#mu[i,1] is the log-odds ratio for study i (1st component of bivariate parameter)
#informative prior for baseline fracture risk, log-odds

alpha_bin[i]~dnorm(-1.2,7)
p[i] <- exp(alpha_bin[i])/(1+exp(alpha_bin[i]))
logit(p[i]) <- alpha_bin[i] + mu[i,1]
rt[i] ~ dbin(p[i], ntb[i])
rc[i] ~ dbin(p[i], ncb[i])
sdLogOR[i] <- sqrt(1/(rc[i]+0.5) + 1/(ncb[i]-rc[i]+0.5) + 1/(rt[i] +0.5) + 1/(ntb[i]-rt[i]+0.5))]

for(i in 1:N)[

#This is the approximate normal likelihood for the data where we now have either
#observed or generated logOR and its variance

precLogOR[i] <- 1/pow(sdLogOR[i],2)
logOR[i] ~ dnorm(mu[i,1] , precLogOR[i])

# continuous outcome: bmd
# Treat the precisions as known

precBMD[i] <- 1/pow(sd[i],2)
D[i] ~ dnorm(deltaBMDgivenlogOR[i], precBMDgivenlogOR[i])

# bivariate outcome: fractures and bmd

deltaBMDgivenlogOR[i] <- mu[i,2] + (sd[i]*rho[i]/sdLogOR[i])*(logOR[i] - mu[i,1])
precBMDgivenlogOR[i] <- 1/VBMDgivenlogOR[i]
VBMDgivenlogOR[i] <- pow(sd[i],2)*(1-pow(rho[i],2))
mu[i,1:2] ~ dmmnor(d[1:2], tau[1:2,1:2])]

#Prior on between-study precision matrix tau
# R is "mean" inverse precision
# 3 is the 'scale'

tau[1:2,1:2] ~ dwish(R[,,]3)
# compute between study variance
v0[1:2,1:2] <- inverse(tau[1:2,1:2])

# compute between-study correlation
cor <- v0[1,2]/sqrt(v0[1,1]*v0[2,2])

# priors on population mean tmt effects
   d[1] ~ dnorm(0,0.0001)
   d[2] ~ dnorm(0,0.0001)
   OR<- exp(d[1])
   d_new[1:2] ~ dmnorm(d[1:2], tau[1:2,1:2])
   newOR<-exp(d_new[1])

# MODEL FOR BETWEEN STUDY VARIANCE MATRIX

# based on Berkey model, no missing data
for(i in 1:k)
   [        z[i,1:2] ~ dmnorm(theta[i,1:2], OMEGA[i,1:2,1:2])
       OMEGA[i,1:2,1:2] <- inverse(W[i,1:2,1:2])
       W[i,1,1] <- sigma1[i]*sigma1[i]
       W[i,2,2] <- sigma2[i]*sigma2[i]
       W[i,1,2] <- sigma2[i]*sigma1[i]*rho_2[i]
       W[i,2,1] <- sigma2[i]*sigma1[i]*rho_2[i]
       theta[i,1:2] ~ dmnorm(phi[1:2], tau[1:2,1:2]) }

   phi[1] ~ dnorm(0,0.0001)
   phi[2] ~ dnorm(0,0.0001)

# PROBABILITIES OF BENEFIT, BOTH OUTCOMES

# ONE OUTCOMES
# Probability of benefit for binary outcome-all fractures
# step function: step (e) = 1 if e >= 0; 0 otherwise
# probability any benefit
   ProbEffect_all_FR_now<-1-step(d[1])
   ProbEffect_all_FR_new<-1-step(d_new[1])

# probability that a decrease is 20%, for OR=0.8
   ProbGE20_FR_now_OR<-step((1-OR) -0.195)
   ProbGE20_FR_new_OR<-step((1-newOR) -0.195)

# Probability of benefit for cont outcome- increase in BMD
# Any effect on LS BMD (>0)
   ProbAny_LS_now<-step(d[2])
   ProbAny_LS_new<-step(d_new[2])

# probability that an increase in LS is 1% (similar to that with vitamin D and calcium)
   ProbGE1_LS_now<-step(d[2] -0.5)
   ProbGE1_LS_new<-step(d_new[2] -0.5)

# BOTH OUTCOMES
# probability of showing any benefit in both outcomes, current and future studies
# p <- equals(x,.7) =1 if x = 0.7, 0 otherwise.
# both <- x * y  
# only x <- equals(x, 1) * equals(y, 0)  
# only y <- equals(x, 0) * equals(y, 1)  
# both <- equals(x, 0) * equals(y, 0)

# current studies: ANY BENEFIT
LS_FR_now <- ProbAny_LS_now * ProbEffect_all_FR_now  
onlyLS_now <- equals(ProbAny_LS_now, 1) * equals(ProbEffect_all_FR_now, 0)  
onlyFR_now <- equals(ProbAny_LS_now, 0) * equals(ProbEffect_all_FR_now, 1)  
both_now <- equals(ProbAny_LS_now, 0) * equals(ProbEffect_all_FR_now, 0)

# future studies: ANY BENEFIT
LS_FR_new <- ProbAny_LS_new * ProbEffect_all_FR_new  
onlyLS_new <- equals(ProbAny_LS_new, 1) * equals(ProbEffect_all_FR_new, 0)  
onlyFR_new <- equals(ProbAny_LS_new, 0) * equals(ProbEffect_all_FR_new, 1)  
both_new <- equals(ProbAny_LS_new, 0) * equals(ProbEffect_all_FR_new, 0)

# probability of both outcomes showing clinically meaningful (realistic) benefit: OR <= 0.8 % BMD increase GE 1%
# current studies: CM BENEFITS
CM_LS_FR_now <- ProbGE1_LS_now * ProbGE20_FR_now * OR  
CM_onlyLS_now <- equals(ProbGE1_LS_now, 1) * equals(ProbGE20_FR_now, 0)  
CM_onlyFR_now <- equals(ProbGE1_LS_now, 0) * equals(ProbGE20_FR_now, 1)  
CM_both_now <- equals(ProbGE1_LS_now, 0) * equals(ProbGE20_FR_now, 0)

# future studies: CM BENEFITS
CM_LS_FR_new <- ProbGE1_LS_new * ProbGE20_FR_new * OR  
CM_onlyLS_new <- equals(ProbGE1_LS_new, 1) * equals(ProbGE20_FR_new, 0)  
CM_onlyFR_new <- equals(ProbGE1_LS_new, 0) * equals(ProbGE20_FR_new, 1)  
CM_both_new <- equals(ProbGE1_LS_new, 0) * equals(ProbGE20_FR_new, 0)

Example of dataset: vitamin K2 : all fractures and lumbar spine BMD

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<th>N</th>
<th>ntb</th>
<th>ntc</th>
<th>rt</th>
<th>rc</th>
<th>logOR</th>
<th>sdLogOR</th>
<th>D</th>
<th>sdD</th>
<th>Rho</th>
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<td>-0.865</td>
<td>0.472</td>
<td>-0.25</td>
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</tr>
</tbody>
</table>

ntb= sample size treatment group; ntc= sample size control group; rt=number of fractures in treatment group; rc=number of fractures in control group; logOR=log odds ratio; sdLogOR= standard deviation of log odds ratio; D= mean difference in BMD; sdD= standard deviation of mean difference; rho= within-study correlation between logOR and D
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