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EU HEALTHCARE COST SAVINGS FROM FOOD SUPPLEMENTS: THE VALUE OF CALCIUM & VITAMIN D AND VITAMIN K2 SUPPLEMENTATION FOR REDUCING OSTEOPOROTIC FRACTURE RISK

A tool for translating nutrient efficacy into consumer health value

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List of abbreviations:

Acronym	Full Term
ARR	Absolute Risk Reduction
BCR	Benefit-Cost Ratio
BMD	Bone Mineral Density
Ca	Calcium
CAGR	Compound Annual Growth Rate
Ca+VitD	Calcium and Vitamin D (combined supplementation)
CI	Confidence Interval
CG	Clinical Guideline
CYP27B1	Cytochrome P450 Family 27 Subfamily B Member 1 (enzyme)
DOAC	Direct Oral Anticoagulant
DRG	Diagnosis-Related Group
DXA	Dual-Energy X-ray Absorptiometry
EFSA	European Food Safety Authority
EER	Experimental Event Rate
EHPM	European Federation of Associations of Health Product Manufacturers
ER	Event Rate
EU	European Union
EUROPOP	Eurostat Population Projections
FRAX	Fracture Risk Assessment Tool
FSE	Food Supplements Europe
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GGCX	Gamma-Glutamyl Carboxylase
GHED	Global Health Expenditure Database
HCCS	Healthcare Cost Savings
HHC	Hospital Healthcare Cost
IOM	Institute of Medicine
INR	International Normalised Ratio
IOF	International Osteoporosis Foundation
MG or MGP	Matrix Gla Protein
MK-4	Menaquinone-4 (short-chain Vitamin K2)
MK-7	Menaquinone-7 (long-chain Vitamin K2)

Acronym	Full Term
NICE	National Institute for Health and Care Excellence
NNT	Number Needed to Treat
NOF	National Osteoporosis Foundation
OC	Osteocalcin
OOP	Out-of-Pocket
OR	Odds Ratio
PAE	Potential Avoidable Events
PPP	Purchasing Power Parity
PTH	Parathyroid Hormone
QALY	Quality-Adjusted Life Year
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
RCT	Randomised Controlled Trial
RR	Relative Risk
RRR	Relative Risk Reduction
SCOPE	Scorecard for Osteoporosis in Europe
T-score	Bone Mineral Density Standard Deviation Score
ucOC	Undercarboxylated Osteocalcin
UK	United Kingdom
VAT	Value Added Tax
VDR	Vitamin D Receptor
VitD	Vitamin D
VitK2	Vitamin K2
VKDP	Vitamin K-Dependent Protein
WHO	World Health Organization
WHI	Women's Health Initiative
YLD	Years Lived with Disability

EXECUTIVE SUMMARY

Osteoporotic fractures represent a substantial and growing consequence of population ageing in Europe. In 2025, an estimated 34.6 million adults across the EU27 and UK were living with osteoporosis, sustaining approximately 4.6 million new fragility fractures annually at a direct hospital cost of €59.9 billion. By 2035, demographic ageing is projected to increase the osteoporosis population to approximately 39.8 million and direct hospital fracture costs to approximately €68.9 billion, under conservative assumptions that hold per-event costs constant over the projection period. Broader societal costs, including long-term disability, productivity losses, informal care and quality-of-life impacts, substantially increase the overall economic burden of osteoporosis. Five countries, Germany, Italy, France, the UK and Spain, account for approximately 66% of the estimated osteoporosis population, although the burden extends across all EU27 countries and the UK.

Country-level treatment gaps remain substantial, averaging approximately 71% across the EU27+UK according to SCOPE 2021. Applying the country-specific treatment-gap estimates to the 2025 osteoporosis population identifies approximately 21.5 million individuals, equivalent to around 62% of the EU27+UK Ca+VitD eligible population, who are estimated to receive no pharmacological treatment for fracture prevention. This substantial treatment gap highlights the potential role of complementary fracture-prevention strategies among individuals estimated to have osteoporosis who are not receiving pharmacological treatment for fracture prevention.

This report quantifies the population-level economic benefit associated with two nutritional interventions: calcium combined with vitamin D (Ca+VitD) and vitamin K2 in the form of menaquinone-7 (MK-7). These interventions operate through distinct biological pathways relevant to bone health. Ca+VitD supports mineral availability and calcium absorption, while vitamin K contributes to the normal maintenance of bones through its role in the carboxylation of vitamin-K-dependent proteins, including osteocalcin.

The cost-savings model follows the established methodological framework of Weaver, Bischoff-Ferrari and Shanahan (2019), updated using 2025 inputs across the EU27 and UK. A consistent six-step clinical pathway translates the efficacy assumptions into estimated avoided fractures and associated healthcare cost savings. The base case adopts a direct hospital cost perspective, capturing acute fracture costs while excluding broader societal costs such as long-term disability, productivity losses, informal care and quality-of-life impacts. A separate sensitivity analysis examines the effect of incorporating long-term disability costs. Under the 100% adoption base case in 2025, Ca+VitD supplementation of the eligible 50+ osteoporosis population, applying a 14% relative risk reduction, is estimated to prevent approximately 644,666 fragility fractures annually. This generates approximately €8.39 billion in gross hospital healthcare cost savings against supplementation expenditure of approximately €2.49 billion, resulting in a €5.90 billion net benefit and a benefit-cost ratio of 3.37. VitK2 supplementation at 180 µg MK-7 daily across the eligible 55+ osteoporosis population, applying a 17% relative risk reduction, is estimated to prevent approximately 743,669 fractures annually. This generates approximately €9.68 billion in gross hospital healthcare cost savings against supplementation expenditure of approximately €4.60 billion, resulting in a net benefit of approximately €5.08 billion and a benefit-cost ratio of 2.11.

Considered across the two independently modelled interventions, Ca+VitD and VitK2 represent approximately 1.39 million avoidable fracture events annually, generating approximately €18.06 billion in gross hospital healthcare cost savings against €7.08 billion in supplementation expenditure and approximately €10.98 billion in net benefit. These combined figures represent the arithmetic sum of the separate intervention scenarios and should not be interpreted as the number of unique fractures that would be prevented through concurrent use of both interventions or as evidence of an additive clinical effect.

The findings remain positive at the EU27+UK aggregate level across the principal sensitivity scenarios tested. Ca+VitD reaches break-even at an RRR of approximately 4.2%, compared with the 14% base-case assumption. VitK2 also remains economically positive at the aggregate level under lower efficacy and higher supplementation-cost assumptions, although its economic return is more sensitive to changes in these parameters because of its higher per-user supplementation cost. Incorporating long-term disability costs further strengthens the economic case for both interventions, as the base-case analysis captures only direct hospital healthcare cost savings.

The geographic distribution of economic benefit varies considerably across the EU27+UK, reflecting differences in fracture incidence, eligible population size, hospital healthcare costs per fracture event and supplementation expenditure. Countries combining high fracture incidence with high treatment costs generally generate stronger economic returns, while the hospital-cost-only benefit-cost ratio is lower in countries where fracture treatment costs are relatively low. This variation highlights the importance of country-specific assessment when considering the economic case for supplementation.

The 2025–2035 projection shows a continued increase in the potential gross healthcare savings associated with avoided fractures. Combined avoided fractures increase from approximately 1.39 million in 2025 to 1.60 million in 2035, while combined gross hospital healthcare cost savings increase from approximately €18.06 billion to €20.79 billion. However, supplementation costs increase faster than gross savings under the model assumptions. As a result, combined net benefit decreases from approximately €10.98 billion in 2025 to €10.34 billion in 2035, while remaining positive throughout the projection period. Over the same period, the Ca+VitD BCR decreases from 3.37 to 2.63 and the VitK2 BCR from 2.11 to 1.64.

The results therefore identify supplementation as a potential component of fracture-prevention strategies with measurable healthcare cost-offset potential, particularly among individuals estimated to have osteoporosis who are not receiving pharmacological treatment for fracture prevention. Under a modelled 71% coverage scenario, reflecting the average country-level treatment gap reported by SCOPE 2021, the two interventions together would prevent approximately 986,000 fractures annually and generate approximately €7.80 billion in net benefit. This scenario represents a sensitivity case rather than the population-weighted proportion of untreated individuals across the EU27+UK, which is lower due to substantial variation in treatment gaps between countries. The magnitude of the opportunity varies considerably between countries and between Ca+VitD and VitK2, supporting a country-specific approach to supplementation policy, reimbursement and implementation.

Parameter	1,000 mg Ca + 600 IU VitD / day	VitK2 MK-7 180 µg/day
Eligible population (million)	34.6	32.9
Fracture risk reduction (RRR)	14%	17%
Average NNT	53.7	44.2
Current annual fractures EU27+UK	4,604,760	4,604,760
Current fracture burden EU27+UK	€59.9bn	€59.9bn
Avoidable fractures per year	644,666	743,669
Gross HCCS (€ billion)	8.387	9.675
Net benefit, 100% coverage (€ billion)	5.9	5.08
Net benefit, 30% coverage (€ billion)	1.8	1.52
Gross return per €1 supplementation	€ 3.37	€ 2.11
Net return per €1 supplementation	€ 2.37	€ 1.11
Average SC/HCCS ratio	29.60%	47.50%

Table ES.1: Summary of Economic Impact by Intervention, EU27+UK, 2025

By 2035, the ageing European population drives both the fracture burden and potential gross healthcare cost savings upward. Combined avoided fractures increase from approximately 1.39 million in 2025 to 1.60 million in 2035, while gross HCCS increases from €8.39 billion to €9.65 billion for Ca+VitD and from €9.68 billion to €11.14 billion for VitK2. Hospital healthcare costs per fracture event are held constant in nominal terms over the projection period, while supplementation costs increase over time.

Consequently, supplementation expenditure grows faster than gross healthcare cost savings, progressively compressing the economic return. Ca+VitD net benefit remains broadly stable, increasing from €5.90 billion in 2025 to a peak of approximately €6.00 billion in 2032 before reaching €5.99 billion in 2035, while its BCR declines from 3.37 to 2.63. VitK2 net benefit declines from approximately €5.08 billion in 2025 to approximately €4.36 billion in 2035, with its BCR decreasing from 2.11 to approximately 1.64. Despite this compression, both interventions remain net positive at the EU27+UK aggregate level throughout the projection period.

Parameter	1,000 mg Ca + 600 IU VitD / day	VitK2 MK-7 180 µg/day
Projected eligible population (million)	39.8	37.8
Projected fracture risk reduction (RRR)	14%	17%
Projected average NNT	54.8	44.9
Projected annual fractures EU27+UK	5,293,693	5,293,693
Projected fracture burden EU27+UK	€68.9 billion	€68.9 billion
Projected avoidable fractures per year	741,117	854,932
Projected gross HCCS (€ billion)	9.653	11.135
Projected net benefit, 100% coverage (€ billion)	5.987	4.356
Projected net benefit, 30% coverage (€ billion)	1.796	1.307
Projected gross return per €1 supplementation	€ 2.63	€ 1.64
Projected net return per €1 supplementation	€ 1.63	€ 0.64
Projected average SC/HCCS ratio	37.90%	60.90%

Table ES.2: Summary of Economic Impact by Intervention, EU27+UK, 2035

PROBLEM STATEMENT

Osteoporotic fractures represent one of the most burdensome, costly, and systematically undertreated public health challenges facing European healthcare systems. In 2025, an estimated 34.6 million adults aged 50 and over across the EU27 and UK have osteoporosis, sustaining approximately 4.6 million new fragility fractures annually, the equivalent of one fracture every seven seconds. At a total direct hospital cost of €59.9 billion in 2025, rising to a projected €68.9 billion by 2035, osteoporotic fractures impose one of the largest acute cost burdens on European healthcare systems of any chronic disease, and with more than 250,000 fracture-related deaths documented across the EU27 and UK in 2019, a mortality burden comparable to or exceeding that of lung cancer, diabetes, and chronic lower respiratory disease, the scale of the problem extends well beyond healthcare expenditure alone.

The scale of the problem is compounded by a substantial treatment gap. Country-level treatment gaps remain high, averaging approximately 71% across the EU27 and UK according to SCOPE 2021. Applying the country-specific treatment-gap estimates to the 2025 osteoporosis population identifies approximately 21.5 million individuals, equivalent to around 62% of the Ca+VitD eligible population, who are estimated to receive no pharmacological treatment for fracture prevention. The treatment gap increased from an average of 55% in 2010 to 71% in 2019. The countries with the largest absolute untreated populations, Italy (3.2 million), Germany (3.1 million), and Spain (2.3 million), are simultaneously among the highest generators of avoidable fracture costs, meaning that the greatest preventive opportunity and the greatest economic return coincide geographically.

The clinical and economic consequences of this gap are severe and compounding. Hip fractures, the most catastrophic fracture type, carry a one-year mortality rate of approximately 20% in women and 37% in men. Of those who survive, approximately 50% never recover their pre-fracture level of function, and one in three requires long-term residential care. Every hip fracture prevented avoids not only the acute hospital episode, itself costing between €2,618 in Slovakia and €19,074 in Sweden, but the downstream care trajectory that can consume multiples of the acute cost over subsequent years. SCOPE 2021 estimated total societal costs of osteoporotic fractures across the EU27 and UK at €56.9 billion in 2019, incorporating acute incident costs of €36.3 billion, long-term disability costs of €19.0 billion, and pharmacological treatment costs of €1.6 billion. When the value of quality-adjusted life years lost is incorporated, the additional burden reached €112.9 billion in the same year.

Looking ahead, the problem will intensify. Europe faces an estimated 25% increase in osteoporotic fractures between 2019 and 2034, from 4.3 million to 5.3 million new fractures annually, driven entirely by the progressive ageing of European populations. By 2035, the EU27 and UK osteoporosis population is projected to reach 39.8 million, with women accounting for approximately 96.8% of the estimated osteoporosis population and the female population with osteoporosis growing by approximately 5.0 million over the decade. Annual fragility fractures are projected to reach approximately 5.3 million by 2035, generating direct hospital costs approaching €69 billion under conservative assumptions that do not account for healthcare cost inflation.

Against this trajectory, the case for preventive nutritional supplementation is both biologically established and economically compelling, yet it remains structurally underutilised.

Two nutritional interventions, calcium combined with vitamin D (Ca+VitD) and vitamin K2 in the form of menaquinone-7 (MK-7), act through distinct but complementary and well-characterised biological mechanisms to address modifiable determinants of bone fragility at the population level. Calcium and vitamin D deficiency is explicitly classified by the WHO Bone Health and Ageing Initiative (2024) as a modifiable risk factor for fragility fractures, placing it alongside smoking, alcohol, and physical inactivity as a correctable population-level deficit rather than an inevitable consequence of ageing. Approximately 58% of Europeans have serum 25-hydroxyvitamin D levels below the threshold associated with adequate bone protection, implying that of the 34.6 million osteoporotic adults in 2025, approximately 20.1 million are vitamin D insufficient, the precise subpopulation in whom Ca+VitD supplementation delivers its most robust clinical benefit. Habitual dietary MK-7 intake across European populations typically falls between 20 and 40 µg per day, well below the 180 µg per day at which osteocalcin gamma-carboxylation, the molecular mechanism through which vitamin K2 anchors calcium into the bone mineral matrix, has been directly demonstrated in clinical trials.

This report quantifies what systematic supplementation of the estimated eligible osteoporosis populations with Ca+VitD and VitK2 would mean in practice: how many fractures would be avoided, at what cost, with what net return to European healthcare systems, and across which countries the economic case is strongest. It does so using a transparent, evidence-anchored methodology updated to 2025 data across all 28 countries of the EU27 and UK, and designed throughout to produce conservative rather than optimistic estimates of intervention value.

The findings are clear: the fracture burden is large, growing, and substantially preventable at a cost that represents a fraction of the healthcare expenditure it would displace.

1. THE BURDEN OF OSTEOPOROTIC FRACTURES IN THE EU27+UK

Osteoporosis is a progressive skeletal disease characterised by low bone mineral density, micro-architectural deterioration of bone tissue, and consequent susceptibility to fracture from minimal or no trauma. In 2025, an estimated 34.6 million adults across the EU27 and UK have osteoporosis, of whom 96.8% are women, a sex asymmetry rooted in the acceleration of bone loss following the oestrogen withdrawal of menopause, which drives bone mineral density decline at a rate five to ten times faster than age-related loss alone. Osteoporosis prevalence rises steeply with age, from approximately 2% of women at age 50 to 12% in the early 60s, 24% in the 70s, and approaching 50% in adults aged 80 and over.

The fracture burden generated by this population is substantial and growing. In 2025, approximately 4.6 million new fragility fractures occur annually across the EU27 and UK, one every seven seconds, rising to a projected 5.3 million by 2035, a 17% increase within a single decade driven entirely by demographic ageing. Five countries, Germany, Italy, France, the UK, and Spain, account for 66% of the total osteoporosis burden and will collectively add approximately 2.9 million additional osteoporotic individuals by 2035. At the other end of the spectrum, Ireland, Cyprus, and Malta face the steepest relative growth, with fracture burdens projected to increase by between 27% and 60% by 2035 as younger populations age into the highest-risk decades.

The direct hospital cost of this fracture burden is equally striking. In 2025, the total direct hospital healthcare costs attributable to incident osteoporotic fractures across the EU27 and UK are estimated at €59.9 billion, up from €36.3 billion documented by SCOPE 2021 for 2019, reflecting both the growth in absolute fracture volume and cumulative healthcare cost inflation across Member States. The cost per fracture event varies 7.3-fold across the region, from €2,618 in Slovakia and €2,641 in Romania to €19,074 in Sweden, a differential that is the primary structural determinant of country-level economic returns to supplementation. By 2035, total direct hospital fracture costs are projected to reach €68.9 billion under conservative assumptions that hold per-event costs constant; applying a realistic healthcare inflation rate of 2–3% annually would push this figure toward €87–92 billion.

Beyond acute hospital costs, the full societal burden is materially larger. SCOPE 2021 estimated total societal costs of osteoporotic fractures at €56.9 billion in 2019, incorporating long-term disability costs of €19.0 billion from hip fracture survivors requiring residential or nursing care, and pharmacological treatment costs of €1.6 billion. When quality-adjusted life years lost are incorporated, the additional burden reached €112.9 billion in the same year. Hip fractures are the principal driver of this downstream cost: approximately 20% of women and 37% of men who sustain a hip fracture die within one year, and of those who survive, approximately 50% never recover their pre-fracture level of function and one in three requires long-term residential care. SCOPE 2021 further documented more than 250,000 fracture-related deaths across the EU27 and UK in 2019, a mortality burden comparable to or exceeding that of lung cancer, diabetes, and chronic lower respiratory disease.

A critical methodological caveat applies throughout: the fracture burden documented here is likely understated. Most vertebral fractures occur without significant trauma or clinical recognition and are

largely absent from the national hospital statistics underpinning SCOPE 2021 incidence data. The true annual fracture burden exceeds the 4.6 million figure used in this report, and all cost estimates derived from it are consequently conservative.

The aggregate picture is unambiguous: osteoporotic fractures impose a large, growing, and insufficiently addressed burden on European healthcare systems, patients, and societies, and the demographic trajectory ensures this burden will intensify throughout the coming decade in the absence of systematic preventive action.

2. TARGET POPULATION

The target population for the supplementation interventions analysed in this report comprises adults estimated to have osteoporosis across the EU27 and UK, with intervention-specific age eligibility criteria. Osteoporosis is defined using the WHO diagnostic standard: a bone mineral density T-score of ≤ -2.5 at the femoral neck or lumbar spine by dual-energy X-ray absorptiometry (DXA). The age threshold and precise population definition differ by intervention, reflecting the clinical evidence base and regulatory standing of each.

For calcium combined with vitamin D (Ca+VitD), the eligible population is adults aged 50 and over estimated to have osteoporosis, consistent with the EU-authorised Article 14 health claim for calcium and vitamin D in reducing the risk of osteoporotic fractures in post-menopausal women, and with the methodology of Weaver, Bischoff-Ferrari, and Shanahan (2019), which applied the same population definition to estimate EU-wide cost-benefit. In 2025, this population totals 34.6 million individuals across the EU27 and UK, of whom 96.8% are women, projected to reach 39.8 million by 2035.

For vitamin K2 in the form of menaquinone-7 (MK-7), the eligible population is adults aged 55 and over estimated to have osteoporosis, reflecting the clinical trial populations in whom MK-7 benefit has been most consistently demonstrated (note: unless otherwise specified, this report uses 50 and over for Ca+VitD and 55 and over for VitK2, consistent with the respective EU claim conditions and clinical trial populations): the Knapen et al. (2013) anchor trial enrolled postmenopausal women with a mean age of 59 years, and the Huang ZB et al. (2015) meta-analysis concentrated its significant findings in women with established osteoporosis rather than the general postmenopausal population. Given the near-negligible prevalence of diagnosed osteoporosis below age 55, this restriction reduces the eligible denominator by approximately 5%, to 32.9 million individuals in 2025, projected to reach 37.8 million by 2035.

Both eligible populations share a common clinical and demographic risk profile that directly underpins the biological rationale for supplementation. Approximately 58% of Europeans have serum 25-hydroxyvitamin D levels below the threshold associated with adequate bone protection, implying that of the 34.6 million osteoporotic adults in 2025, approximately 20.1 million are vitamin D insufficient, the physiological condition under which Ca+VitD supplementation delivers its most robust and consistently demonstrated clinical benefit. Habitual dietary MK-7 intake across European populations typically ranges from 20 to 40 μg per day from fermented food sources, well below the 180 μg per day at which osteocalcin gamma-carboxylation has been directly demonstrated in postmenopausal women, and below the 90–180 μg per day required for meaningful improvement in extra-hepatic VKDP carboxylation (Theuvsen et al. 2012; Westenfeld et al. 2012). Crucially, the circulating levels of MK-7 required to reduce undercarboxylated osteocalcin increase with age, precisely when the eligible population is entering its highest fracture-risk period, creating a structural micronutrient gap that dietary sources alone are unlikely to close.

The treatment gap defines where supplementation carries its greatest incremental value. In 2025, approximately 21.5 million individuals estimated to have osteoporosis across the EU27 and UK, 62% of the total Ca+VitD eligible population, are estimated to be receiving no pharmacological treatment for

fracture prevention. This population remains exposed to osteoporotic fracture risk without pharmacological treatment for fracture prevention, and represents the primary addressable opportunity for Ca+VitD and VitK2 supplementation. Reaching even this untreated subpopulation, rather than the full eligible population, would prevent over 985,000 fractures annually and generate a combined net healthcare benefit of €7.8 billion per year at current supplement prices across the EU27 and UK.

3. CALCIUM AND VITAMIN D OSTEOPOROTIC FRACTURE RISK REDUCTION PATHWAY

Osteoporotic fractures are largely preventable. Two nutritional interventions, calcium combined with vitamin D, and vitamin K2 in the form of menaquinone-7 (MK-7), act through distinct but complementary biological mechanisms to address modifiable determinants of bone fragility at the population level.

Calcium and vitamin D deficiency is explicitly listed by the WHO Bone Health and Ageing Initiative (2024)¹ as a modifiable risk factor for fragility fractures, alongside smoking, alcohol consumption, and physical inactivity, establishing supplementation not as an optional wellness measure but as a targeted response to a recognised, population-level, correctable deficit.

Vitamin K2 (MK-7) operates through a separate and non-redundant pathway: it activates the gamma-carboxylation machinery responsible for anchoring calcium into the bone mineral matrix via osteocalcin, a process that is independent of calcium and vitamin D supply and therefore complementary in populations where both the mineral substrate and the activation pathway are suboptimal.

The following section documents, for each intervention, the complete fracture risk reduction pathway, from the eligible population through the biological mechanism, the clinical evidence base, the regulatory standing, and the step-by-step translation into quantifiable avoided fractures and net healthcare cost savings across all 28 countries of the EU27 and UK.

3.1. Overview and positioning

Calcium and vitamin D are the most extensively studied nutritional interventions for bone health and represent the foundational supplementation strategy for osteoporosis prevention and management. The evidence base spans more than three decades of randomised controlled trial evidence, systematic reviews, and meta-analyses, with a consistent finding: combined supplementation at adequate doses reduces the overall risk of osteoporotic fractures by 14% in adults aged 50 and over. This effect size, derived from the National Osteoporosis Foundation meta-analysis by Weaver et al. (2016), anchors the cost-savings model presented in this report and provides the methodological precedent for the present report.

The intervention is not novel. The first landmark randomised controlled trial demonstrating fracture risk reduction, Chapuy et al. (1992) in institutionalised elderly French women receiving 1,200 mg calcium and 800 IU vitamin D3 daily, reported a 43% reduction in hip fractures and 32% reduction in non-vertebral fractures over 18 months.²

More than three decades and dozens of trials later, the evidence base remains the most robust of any nutritional intervention for fracture prevention, while also remaining subject to genuine scientific

¹ [WHO Bone Health and Ageing Initiative](#) (2024)

² Weaver CM et al, Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation, *Osteoporosis Int.* 2015 Oct 28;27:367–376

controversy regarding the conditions under which benefit is most reliably demonstrated. This section addresses both the strength of the evidence and the conditions that determine where it applies.

3.2. Primary Event/Fracture Outcomes

The primary outcome of interest is fracture incidence, a hard clinical endpoint directly translatable to healthcare costs. Unlike other interventions evidence chains which require a two-step inference from biomarker change to clinical event, calcium and vitamin D supplementation has been tested directly against fracture incidence as a primary endpoint across multiple large RCTs. The evidence base comprises more than 50 RCTs and a corresponding literature of systematic reviews and meta-analyses, the most policy-relevant of which are reviewed here with attention to the most recent publications.

The primary model input is the Weaver et al. (2016) National Osteoporosis Foundation meta-analysis,^{3,4} which pooled 7 RCTs covering 26,625 participants and 1,763 fracture events, yielding a pooled relative risk for total fractures of 0.86 (95% CI: 0.75–0.98), a statistically significant 14% relative risk reduction. (Note: the original Weaver et al. 2015 paper reported RR 0.85 (15% RRR); the 2016 erratum revised this to RR 0.86 (14% RRR), and this corrected figure is used throughout the model.) This meta-analysis was applied directly to the EU population by Weaver, Bischoff-Ferrari, and Shanahan in the peer-reviewed cost-benefit analysis that provides the methodological precedent for the present report, estimating 544,687 prevented fractures per year and a net cost benefit of approximately €5.7 billion annually across the EU27.²

The most recent evidence is consistent with this population-specificity pattern. A 2025 systematic review and meta-analysis by Cong and Zhang (11 RCTs, 43,869 participants) in 2025 restricted to postmenopausal women with osteoporosis found no statistically significant reduction in overall clinical fracture risk with combined calcium and vitamin D supplementation (RR 0.98; 95% CI: 0.89–1.07), a neutral result driven by three large trials enrolling participants across a wide range of baseline vitamin D status and fracture risk. This finding is consistent with the broader pattern in the literature: fracture benefit is most reliably demonstrated in populations with confirmed vitamin D insufficiency and diagnosed osteoporosis, and is diluted or absent when trials pool supplemented and replete individuals together. The Cong and Zhang result therefore reinforces the model's eligible population definition by restricting the denominator to diagnosed osteoporotic adults aged 50 and over. The model applies the

³ Chapuy MC et al. "Vitamin D3 and calcium to prevent hip fractures in the elderly women." *New England Journal of Medicine* 1992;327(23):1637–1642.

⁴ Weaver CM et al, Erratum and additional analyses re: Calcium plus vitamin D supplementation and the risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation, *Osteoporosis Int.* 2016 Jul 11;27(8):2643–2646

14% RRR precisely to the subpopulation in whom clinical benefit is concentrated, and not to the broader mixed-risk population in whom it is not.⁵

For hip fractures specifically, meta-analyses consistently report reductions of 25–30% when adequate doses are combined, with the Chapuy 1992³ trial reporting 43% and the pooled systematic review by Manoj P et al. (2023) reporting an odds ratio of 0.69 (95% CI: 0.58–0.82) for hip fracture at 800 IU vitamin D3 plus 1,200 mg calcium.⁶

The literature is not uniformly positive, and this report does not selectively cite only favourable results. A JAMA meta-analysis by Zhao et al. of 33 trials in community-dwelling older adults found no significant reduction in fractures with the combination.⁷ A 2024 meta-analysis by de Moura de Souza et al. of 7 RCTs in 71,899 patients without bone-related conditions found no significant total fracture reduction with vitamin D supplementation alone.⁸ The resolution of this apparent contradiction is established and clinically meaningful: fracture benefit is most reliably demonstrated in populations with vitamin D insufficiency and in individuals with diagnosed osteoporosis, at doses of 800 IU or above combined with adequate calcium, precisely the eligible population and dose conditions defined in this report and in the EU-authorized claim.

3.3. Dose-response relationship

The dose-response relationship for calcium and vitamin D fracture prevention is clearly characterised across the literature and directly determines the conditions under which the model's 14% RRR applies.

For vitamin D, a consistent dose threshold is established: doses below 700 IU/day show no significant fracture benefit across trials, while doses of 700–800 IU/day combined with calcium show consistent benefit in high-risk populations, and doses of 800–2,000 IU/day are associated with the most robust reductions in falls and hip fractures, particularly in individuals with baseline deficiency.

⁵ Bo Cong and Haiguang Zhang, The effects of combined calcium and vitamin D supplementation on bone mineral density and fracture risk in postmenopausal women with osteoporosis: a systematic review and meta-analysis of randomized controlled trials, BMC Musculoskelet Disord. 2025 Oct 8;26:928

⁶ Manoj P et al., What is the impact of daily oral supplementation of vitamin D3 (cholecalciferol) plus calcium on the incidence of hip fracture in older people? A systematic review and meta-analysis. Int J Older People Nurs. 2023 Jan;18(1):e12492

⁷ Jia-Guo Zhao et al. , Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. JAMA . 2017 Dec 26;318(24):2466-2482

⁸ Moura de Souza et al., Vitamin D Supplementation and the Incidence of Fractures in the Elderly Healthy Population: A Meta-analysis of Randomized Controlled Trials, J Gen Intern Med 2024 Nov;39(14):2829-2836.

A 2022 meta-analysis⁹ stratified by dose found that vitamin D3 at 800–1,000 IU/day reduced fractures by 13% and falls by 19%. Intermittent high-dose regimens, annual or quarterly bolus dosing, do not produce equivalent benefit and in some analyses are associated with paradoxical increases in fall risk, confirming that sustained daily supplementation is the clinically relevant delivery mode.

This distinction between daily supplementation and intermittent bolus dosing has been independently characterised in a 2025 peer-reviewed review in *Frontiers in Nutrition* as a common methodological oversight that explains conflicting results across vitamin D intervention studies. Christie et al. (2025) note that high-dose bolus vitamin D, for example, 100,000 IU in a single dose, as opposed to a physiologically favourable daily lower dose, can lead to false negative outcomes or nil treatment effects, and that the current consensus is that pharmacological-strength bolus doses of vitamin D are limited in their applications in research settings. This methodological point has direct relevance to the interpretation of meta-analyses that pool trials using different delivery modes: studies using bolus regimens systematically dilute the observed effect size of daily supplementation, and their inclusion in pooled analyses contributes to the heterogeneity that has led some reviewers to question the fracture prevention evidence base. The Weaver et al. (2016) meta-analysis used as the primary model input in this report draws on RCTs using daily or near-daily supplementation protocols, not bolus regimens, and the 14% RRR it reports should therefore be understood as the effect size applicable to the clinically relevant delivery mode rather than a diluted average across methodologically mixed trial designs.

The dose distinction in the evidence base requires explicit acknowledgment. The most clearly demonstrated hip fracture benefit, OR 0.69 (95% CI: 0.58–0.82), is associated with 800 IU vitamin D3 combined with 1,200 mg calcium, while the same vitamin D dose at 1,000 mg calcium produced no significant effect (OR 1.08; 95% CI: 0.74–1.56). The model uses 1,000 mg calcium and 600 IU vitamin D, the minimum daily dose specified in the EU-authorised Article 14 health claim and the dose applied in the Weaver et al. (2019) EU cost-benefit analysis that provides the methodological precedent for this report. This dose sits at the lower end of the effective range rather than at its peak. Two considerations justify applying the 14% total fracture RRR from Weaver et al. (2016) at this dose. First, the Weaver 2016 pooled meta-analysis was itself conducted across RCTs using a range of doses, and the 14% RRR represents the average effect across that distribution, it is not derived exclusively from the highest-dose trials. Second, the 14% figure applies to total fractures, not specifically to hip fractures; the dose-response gradient is steeper for hip fractures than for non-vertebral and vertebral fractures, meaning the total fracture effect at the model dose is less sensitive to the calcium threshold than the hip fracture subgroup data suggest. The model therefore does not claim to reproduce the peak hip fracture efficacy demonstrated at 1,200 mg calcium, and the 14% total fracture RRR should be understood as applicable

⁹ Fleet JC (2022), Fleet JC. "Vitamin D-Mediated Regulation of Intestinal Calcium Absorption." *Nutrients* 2022;14(16):3351

and defensible at the modelled dose, while acknowledging that higher doses would likely produce larger absolute risk reductions.

Tang et al. (2007), in a meta-analysis of 29 RCTs covering 63,897 participants aged 50 and over, reported a 12% reduction in total fracture risk across studies using calcium alone or in combination with vitamin D, with the largest effects observed in older, institutionalised populations with low baseline calcium intake and low serum 25(OH)D, precisely the characteristics that define the vitamin D-insufficient, diagnosed osteoporotic eligible population in this model.¹⁰ This dose-gradient pattern is consistent with the model's expectation that the 14% RRR, derived from the Weaver et al. (2016) pooled analysis across a distribution of doses, is applicable and defensible at 1,000 mg calcium and 600 IU vitamin D, while acknowledging that supplementation at higher doses, 1,200 mg calcium and 800 IU vitamin D, would be expected to produce larger absolute risk reductions in the eligible population. Within this pooled dataset, fracture risk reduction was significantly greater at calcium doses of 1,200 mg or above compared with doses below 1,200 mg ($p=0.006$), and at vitamin D doses of 800 IU or above compared with doses below 800 IU ($p=0.03$), confirming that the modelled dose is conservative relative to what higher doses would be expected to produce.¹⁰

The synergistic requirement of both nutrients together is a consistent finding. Calcium supplementation alone does not significantly reduce fracture risk in RCTs. Vitamin D supplementation alone reduces falls but shows more mixed results on fractures, particularly in populations without severe deficiency. The combination is required to activate both mechanisms, substrate supply and absorption regulation, simultaneously, which is the biological rationale for the [EU-authorised Article 14 claim](#) requiring both nutrients.

3.4. Mechanism of Action

The biological mechanism operates through two established and complementary pathways, both confirmed in clinical studies at the doses modelled in this report.

3.4.1. Pathway 1: Calcium absorption and PTH suppression cascade

Vitamin D insufficiency, defined as serum 25(OH)D below 50 nmol/L, affects an estimated 40–58% of the general European population, a prevalence described as reaching pandemic levels across Europe (Lips et al. 2019; Amrein et al. 2020; Christie et al. 2025), rising to approximately 80% in institutionalised elderly adults (Spiro et al. 2014), and likely a higher proportion among the elderly osteoporotic population. This insufficiency impairs activation of intestinal vitamin D receptors, reducing active transcellular calcium

¹⁰ Tang et al, Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis, Lancet 2007 Aug 25;370(9588):657-66

transport in the duodenum and jejunum.¹¹ The consequent fall in serum ionised calcium triggers compensatory PTH secretion by the parathyroid glands. Chronically elevated PTH drives osteoclastic bone resorption through upregulation of RANKL expression by osteoblasts, mobilising skeletal calcium reserves to restore serum calcium, at the progressive cost of bone mineral density. Vitamin D supplementation at 800 IU or above restores 25-hydroxyvitamin D to the range associated with adequate VDR activation, normalising intestinal calcium absorption and removing the physiological stimulus for PTH-driven resorption. Calcium supplementation simultaneously increases the circulating substrate available for mineralisation and independently suppresses PTH secretion through calcium-sensing receptor activation in the parathyroid glands.

Chapuy et al. directly confirmed that combined calcium and vitamin D3 supplementation reverses secondary hyperparathyroidism in elderly institutionalised women, with femoral neck BMD preserved in the supplemented group (mean change +0.29% per year) versus declining in placebo (−2.36% per year).¹² A 2025 peer-reviewed review in *Frontiers in Nutrition* independently characterises the prevalence of vitamin D insufficiency across Europe as a public health crisis that remains under-recognised among policymakers and healthcare providers, and identifies vitamin D as the paradigm case for the broader failure to address micronutrient insufficiency through available and cost-effective interventions including food supplementation (Christie et al. 2025). This institutional under-recognition is directly relevant to the model's policy argument: the biological mechanism described above has been established for decades, the eligible population experiencing it is quantified at 34.6 million across the EU27 and UK, and the cost-effective intervention exists at a weighted average of €71.85 per user per year, yet the majority of that population remains unsupplemented.

3.4.2. Pathway 2: Vitamin D and bone-forming cells

Vitamin D receptors are expressed in osteoblasts and osteocytes, and extrarenal activation of 1,25-dihydroxyvitamin D in bone tissue has been linked to osteoblast progenitor formation, supporting bone formation independent of the systemic calcium absorption effect. This dual action, reducing resorption by interrupting PTH-driven osteoclast activation, and supporting formation through direct VDR signalling

¹¹ Lips P et al. Vitamin D status and nutrition in Europe and Asia. *J Steroid Biochem Mol Biol.* 2019;187:62–66. Amrein K et al. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr.* 2020;74(11):1498–1513.

¹² Chapuy MC et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study." *Osteoporosis International* 2002;13(3):257–264.

in osteoblasts, explains why combined Ca+VitD produces clinically meaningful fracture risk reduction that neither nutrient achieves alone.¹³

Beyond mineral supply, vitamin D exerts direct actions on bone-forming and bone-remodelling cells because chondrocytes, osteoblasts, osteocytes, and osteoclasts all express vitamin D receptors (VDR) and the enzyme CYP27B1, enabling local activation and response. In growth plate cartilage, vitamin D promotes hypertrophic chondrocyte differentiation, alkaline phosphatase activity, matrix vesicle production, and cartilage calcification, all of which are essential for normal endochondral ossification and longitudinal bone growth. In osteoblasts, vitamin D regulates genes involved in matrix production and mineralisation, including osteocalcin and osteopontin, while modulating osteoblast maturation and mineral apposition. A central component of this process is vitamin D-induced alkaline phosphatase activity, which hydrolyses pyrophosphate, a major inhibitor of mineral deposition, thereby facilitating phosphate release and calcium-phosphate crystal formation within the collagen matrix.

Overall, vitamin D functions as both a regulator of mineral supply and a local skeletal hormone. While adequate calcium and phosphate intake can partially compensate for deficiency, optimal bone mineralisation depends on sufficient vitamin D to coordinate mineral availability, growth plate maturation, osteoblast function, and remodelling. This integrated mechanism explains why vitamin D is indispensable not only for preventing overt bone disease but also for maintaining long-term bone density and structural integrity.¹⁴

3.5. The Fracture Risk Reduction Pathway

The complete chain from supplementation to prevented fractures and avoided costs in the model runs as follows. The eligible population, an estimated 34.6 million adults aged 50 and over with osteoporosis across the EU27 and UK in 2025, carries an annual fracture event rate averaging 14.5% across countries, ranging from 9.6% in Romania and Estonia to 28.8% in Slovakia. Supplementation at 1,000 mg calcium and 600 IU vitamin D daily applies the model's 14% relative risk reduction to each country's fracture event rate, generating an absolute risk reduction (ARR) equal to the event rate multiplied by 14%. At the EU27+UK aggregate level this yields an ARR of approximately 1.3–4.0% across countries, translating to a number needed to treat (NNT) of approximately 25 supplemented individuals per year in Slovakia to 74 in Romania to prevent one fracture.

¹³ van Driel et al., Vitamin D and Bone: A Story of Endocrine and Auto/Paracrine Action in Osteoblasts, *Nutrients* 2023, 15, 480

¹⁴ Daniel D. Bikle, Vitamin D and Bone, *Curr Osteoporos Rep.* 2012 June ; 10(2): 151–159

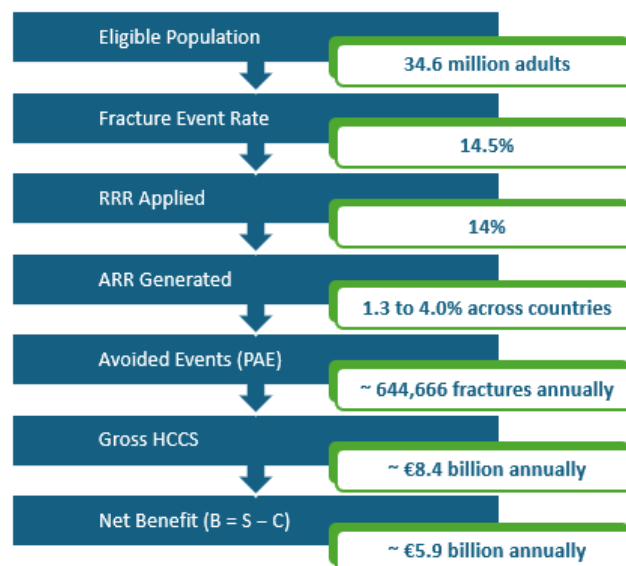


Figure 4.5.1: The Fracture Risk Reduction Pathway

Multiplying the ARR by the osteoporosis population in each country yields the potential avoidable fracture events (PAE), totalling approximately 644,666 fractures annually across the EU27+UK at 100% adoption in 2025. Multiplying avoided events by the country-specific hospital healthcare cost per fracture event, ranging from €2,641 in Romania to €19,074 in Sweden, yields gross healthcare cost savings of approximately €8.4 billion annually at the EU27+UK level.

Subtracting the cost of supplementing the entire eligible population, at country-specific annual costs ranging from approximately €48 (Latvia) to €174 (Luxembourg) per user, yields a total supplementation cost of €2.5 billion and a net population benefit of approximately €5.9 billion annually across the EU27+UK. The benefit-cost ratio ranges from 0.62 in Romania, where the hospital cost saved per prevented fracture does not offset the annual supplement cost under the hospital-cost-only framework, to 7.05 in Sweden, where avoiding a single fracture saves more than seven times the annual supplement cost per user.

These figures represent conservative lower bounds. The model captures only direct hospital healthcare costs of incident fractures, excluding long-term disability costs, nursing home placement, lost productivity, informal carer burden, and the value of quality-adjusted life years lost. SCOPE 2021 estimated total societal costs of osteoporotic fractures across the EU27+UK at €56.9 billion in 2019, incorporating acute incident costs of €36.3 billion and long-term disability costs of €19.0 billion. Under an ****expanded direct healthcare cost perspective**** applying the SCOPE 2021 disability cost multiplier, the Ca+VitD net population benefit increases to approximately €10.29 billion annually, and all country-level negative net benefit figures are eliminated. The full country-level breakdown, sensitivity analysis across alternative RRR values, population coverage rates and cost perspectives, and the 2025–2035 projection are presented in the Cost-Savings Modelling chapter.

3.6. Safety profile, updated risk quantification

The safety profile of combined calcium and vitamin D supplementation at the doses modelled in this report is well-established and broadly favourable across the adult population including adults aged 50 and over with osteoporosis.

3.6.1. Vitamin D3 (cholecalciferol) has a broad therapeutic index

Toxicity requires sustained serum 25-OH-D levels above 150–200 ng/mL, achievable only with prolonged supplementation substantially exceeding the doses under consideration. At 600–800 IU/day, supplementation is safe in adults including the elderly, with the 2024 Endocrine Society Clinical Practice Guideline endorsing empirical supplementation for healthy adults aged 75 and over at an average of 900 IU/day, higher than the model dose. Paradoxical harm has been observed only with very high intermittent dosing (annual bolus regimens of 500,000 IU or quarterly doses), which are outside the scope of daily food supplement use. EFSA has established a tolerable upper intake level of 4,000 IU/day for vitamin D in adults, substantially above the 600–800 IU/day modelled in this report, confirming the broad safety margin at supplementation doses. The 800–2,000 IU/day range associated with the most robust reductions in falls and hip fractures (see section 4.3) sits well within this safety envelope.¹⁵

3.6.2. Calcium supplements considerations at the doses modelled in this report.

First, gastrointestinal tolerability: calcium carbonate is associated with constipation and flatulence at rates that materially reduce adherence in clinical trials, with reported adherence as low as 55–63% in some included studies. Calcium carbonate provides the highest proportion of elemental calcium per tablet and is generally well-tolerated when taken with meals, as food-stimulated gastric acid production improves absorption and reduces GI side effects (Amarnath et al. 2023). The tolerability issues described above are primarily associated with fasting administration. Calcium citrate offers substantially improved tolerability and is preferred in individuals with achlorhydria or proton pump inhibitor use.

Second, nephrolithiasis: the WHI (Jackson et al. 2006) reported an increase of 5.7 events per 10,000 person-years in women receiving 1,000 mg calcium combined with 400 IU vitamin D, a population with above-average baseline calcium intake. This risk is modest in absolute terms, concentrated in individuals with pre-existing stone risk, and reduced by splitting calcium doses to 500 mg or less and maintaining adequate hydration.

¹⁵ Marie B Demay et al., Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline Free, The Journal of Clinical Endocrinology & Metabolism, 2024, 109, 1907–1947

Third, cardiovascular risk: concern raised by Bolland et al. regarding myocardial infarction has been substantially qualified by subsequent analysis.^{16,17} The signal is associated with calcium supplementation alone without vitamin D co-administration, at doses above routine supplementation, and in populations without vitamin D insufficiency. The joint clinical guideline by the National Osteoporosis Foundation and the American Society for Preventive Cardiology¹⁸ concluded that calcium and vitamin D supplementation up to 2,000 mg/day does not significantly increase cardiovascular, cerebrovascular, or mortality risk in generally healthy adults.

Updated Risk Quantification

The most current quantification of net benefit from calcium and vitamin D supplementation in the EU context is provided by Weaver, Bischoff-Ferrari, and Shanahan,² which remains the most rigorous peer-reviewed cost-benefit analysis covering the EU to date. Using 2016–2017 data, this analysis estimated €5.7 billion net annual benefit in the EU from universal supplementation of the osteoporotic population at 1,000 mg calcium and 600 IU vitamin D, with a benefit-cost ratio of €5.58 saved per €1 spent on supplements.

Updated to 2025 data in the present report, reflecting growth in the osteoporosis population, price inflation in fracture healthcare costs, and current supplement retail pricing, the EU27+UK net annual benefit is estimated at approximately €5.9 billion for Ca+VitD and €5.08 billion for VitK2 under the 100% adoption scenario, with benefit-cost ratios ranging from 0.62 to 7.05 for Ca+VitD across countries, from Romania, where the HHC per fracture event falls below the supplement cost threshold, to Sweden, where avoiding a single fracture saves more than seven times the annual supplement cost per user. The total eligible population in 2025 is estimated at 34.6 million individuals with osteoporosis across the EU27 and UK, sustaining 4.6 million new fragility fractures annually at a direct hospital cost of approximately €59.9 billion.

¹⁶ Bolland MJ et al., Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691

¹⁷ Bolland MJ et al. ,Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011;342:d2040.

¹⁸ Stephen L. Kopecky et al., Lack of Evidence Linking Calcium With or Without Vitamin D Supplementation to Cardiovascular Disease in Generally Healthy Adults: A Clinical Guideline From the National Osteoporosis Foundation and the American Society for Preventive Cardiology, *Ann Intern Med.* 2016 Dec 20;165(12):867-868

4. VITAMIN K2 (MENAQUINONE-7) OSTEOPOROTIC FRACTURE RISK REDUCTION PATHWAY

4.1. Overview and Positioning

Vitamin K2, specifically the menaquinone-7 (MK-7), is a nutritional intervention with a distinct and increasingly well-characterised role in bone health that operates independently of and complementarily to the calcium and vitamin D pathway.

Where calcium and vitamin D address the availability and absorption of mineral substrate for bone formation, vitamin K2 activates the molecular machinery responsible for anchoring that calcium into the bone mineral matrix. The two pathways are therefore not redundant but sequential: calcium must first be absorbed and transported to bone tissue through the Ca+VitD mechanism and then incorporated into the hydroxyapatite crystal lattice through the vitamin K2-dependent carboxylation of osteocalcin. A population deficient in both pathways, as a substantial proportion of the European elderly osteoporotic population is, cannot achieve optimal bone mineralisation from either intervention alone.^{12,19}

The regulatory standing of vitamin K2 for bone health in the EU is established but distinct from that of calcium and vitamin D. The European Food Safety Authority has authorised an Article 13(1) general function health claim under EU Regulation 432/2012 (European Commission 2012; EFSA NDA Panel 2009), confirming that vitamin K contributes to the maintenance of normal bones at a minimum of 75 µg per daily serving from food supplements. No Article 14 fracture risk reduction claim has been authorised by EFSA for vitamin K2, reflecting the current state of the clinical evidence base rather than a biological implausibility, the mechanism is well-established, the biomarker evidence is consistent, and the fracture signal in meta-analyses is positive, but the RCT evidence powered specifically for fracture as a primary endpoint at supplement-relevant MK-7 doses in European populations is not yet available at the level required for Article 14 authorisation.

A placebo-controlled dose-finding study testing daily MK-7 doses of 10, 20, 45, 90, 180, and 360 µg demonstrated that doses from 90 µg/day significantly improved osteocalcin carboxylation, with near-maximal effect approaching at 180 µg/day (Theuvsissen et al., Br J Nutr 2012;108(9):1652–7).

The dose modelled in this report, 180 µg/day MK-7, reflects the anchor clinical trial dose from Knapen et al. and exceeds the EFSA minimum, consistent with the dose at which osteocalcin gamma-carboxylation has been directly demonstrated in healthy postmenopausal women.²⁰

¹⁹ Bertolacini da Silva T et al. Supplements for bone health, Archives of Endocrinology and Metabolism 2026; 70 (special issue 1):e2025-0374

²⁰ M H J Knapen et al., Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women, Osteoporos Int. 2013 Sep;24(9):2499-507.

4.2. Primary Event Outcomes

The primary clinical question for the cost-savings model is whether vitamin K2 supplementation at supplement-relevant MK-7 doses reduces the incidence of osteoporotic fractures in the eligible population. The honest characterisation of the evidence is that the fracture signal is positive and consistent across the meta-analytic literature but is not as definitively established as the Ca+VitD evidence chain, a distinction this section addresses.

The most directly relevant meta-analysis is Huang ZB et al.,²¹ which pooled 19 randomised controlled trials covering 6,759 postmenopausal women using MK-4 (1.5–90 mg/day) or MK-7 (100–360 µg/day). The pooled analysis for fracture incidence found no statistically significant difference between supplemented and unsupplemented groups in the primary intent-to-treat analysis. However, a subsequent sensitivity analysis demonstrated a significant benefit favouring vitamin K2 supplementation, a result that is methodologically important because it is consistent with the hypothesis that fracture benefit in this evidence base is concentrated in specific subpopulations, principally women with established osteoporosis rather than the general postmenopausal population. This population specificity directly aligns the Huang 2015 evidence with the model's eligible population of diagnosed osteoporotic adults aged 50 and over.

Salma et al.,²² a systematic review and meta-analysis incorporating studies from Asia, North America, Europe, and Africa using vitamin K1 (100 µg to 5 mg) or K2 (180 µg to 45 mg) for 6–36 months, found a decrease in overall fracture risk in the group receiving vitamin K supplementation. Critically, K2 forms at higher doses showed a more pronounced anti-fracture effect, and the effect on fracture risk was observed even in studies showing minimal impact on BMD, suggesting a mechanism of fracture prevention that extends beyond simple bone density preservation, potentially through improved bone quality and matrix organisation. Hu L et al.,²³ a meta-analysis of 10 RCTs comparing the combined effect of vitamin K and calcium versus control groups, found that the combination was associated with increased lumbar BMD and reduced levels of undercarboxylated osteocalcin, a direct biomarker of vitamin K2 activity at the bone tissue level. This paper is particularly relevant to the present report because it addresses the combination of VitK2 with calcium, the co-supplementation context in which MK-7 is most likely to be used by the eligible population.

²¹ Z-B Huang, Does vitamin K2 play a role in the prevention and treatment of osteoporosis for postmenopausal women: a meta-analysis of randomized controlled trials, *Osteoporos Int.* 2015 Mar;26(3):1175-86

²² Salma et al., Effect of Vitamin K on Bone Mineral Density and Fracture Risk in Adults: Systematic Review and Meta-Analysis, *Biomedicines* 2022, 10(5), 1048

²³ Liyou Hu et al., The combined effect of vitamin K and calcium on bone mineral density in humans: a meta-analysis of randomized controlled trials, *J Orthop Surg Res.* 2021 Oct 14;16:592

The broader epidemiological evidence supports the fracture risk association. A meta-analysis by Hao G et al. covering over 80,000 participants demonstrated that both low dietary intake and low circulating levels of vitamin K are associated with reduced bone mineral density and an increased risk of fractures, particularly of the hip.²⁴ Booth SL et al.,²⁵ using Framingham Heart Study data,²⁶ identified an association between low dietary vitamin K intake and elevated hip fracture risk in women and reduced bone mineral density in both sexes. These observational findings establish the population-level relevance of vitamin K status to fracture outcomes and provide independent epidemiological support for the intervention logic.

The Cockayne et al. meta-analysis which reported pooled fracture risk reductions of 60% for vertebral fractures and 77% for hip fractures with vitamin K2, is not used as a primary evidence source in this report because the pooled estimate is dominated by Japanese MK-4 trials at 45 mg/day, a pharmacological dose approximately 250 times higher than the 180 µg/day MK-7 dose modelled here, and is not transferable to EU food supplement practice.²⁷

4.3. Dose-Response Relationship

The dose-response relationship for vitamin K2 fracture prevention is clinically important and substantially different from the Ca+VitD evidence base in one critical respect: the available RCT evidence is distributed across two structurally distinct dosing regimes, *MK-4 at pharmacological doses* (1.5–90 mg/day) dominated by Japanese trials, and *MK-7 at nutritional supplement doses* (100–360 µg/day), and these cannot be treated as equivalent.

For MK-7, the relevant dose-response data centre on the 180 µg/day dose used in the Knapen et al. trial, the anchor clinical study for this report.²⁰ In this 3-year double-blind RCT of 244 healthy postmenopausal women (mean age 59 years), daily supplementation with 180 µg MK-7 significantly reduced the age-related decline in bone mineral content and bone mineral density at the lumbar spine and femoral neck compared to placebo. The ratio of undercarboxylated to total osteocalcin, the validated biomarker of vitamin K2 biological activity at bone, was significantly reduced, confirming that the 180 µg/day dose was biologically active at the bone tissue level. This dose-biomarker confirmation is the most important finding from a model defensibility perspective: it establishes that 180 µg/day MK-7 achieves the

²⁴ Guangliang Hao et al., Vitamin K intake and the risk of fractures: A meta-analysis, *Medicine* (Baltimore). 2017 Apr;96(17):e6725

²⁵ Booth SL et al., Vitamin K intake and bone mineral density in women and men, (2003, *Am J Clin Nutr* 77:512–516

²⁶ The Framingham Heart Study (FHS) is an epidemiologic study begun in Framingham in 1948 with 5,209 men and women. Since that time the FHS has studied three generations of participants resulting in biological specimens and data from nearly 15,000 participants.

²⁷ Cockayne et al. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials, 2006, *Arch Intern Med* 166:1256–1261

intended pharmacological target in the bone matrix, independent of the question of whether fracture reduction has been directly demonstrated.

The relationship between MK-7 dose and osteocalcin carboxylation is characterised by a saturation curve: doses below approximately 90–100 µg/day produce incomplete carboxylation of circulating osteocalcin, while doses of 180–200 µg/day achieve near-maximal carboxylation in most postmenopausal women. Studies on the relationship between ucOC reduction and bone outcomes consistently find that greater carboxylation, achieved at higher doses, is associated with better bone mineral density outcomes and lower fracture risk in observational data.²⁸ Doses of 90–180 µg/day have been shown to significantly improve carboxylation of both osteocalcin and MGP (Theuwissen et al. 2012; Sato et al. 2020), confirming that the modelled dose sits at or above the threshold for biologically meaningful effect on both principal VKDPs. The model dose of 180 µg/day MK-7 therefore sits at the clinically validated threshold for meaningful biological effect, not at a sub-effective nutritional dose.

The Huang ZB et al. meta-analysis,²¹ which covered MK-7 doses from 100 to 360 µg/day across 19 RCTs, found significantly improved lumbar BMD among Japanese patients with osteoporosis but not in non-osteoporotic groups (see section 5.2 for full discussion of fracture outcomes from this meta-analysis).

This population-dose interaction is important: the bone benefit of MK-7 supplementation is most consistently demonstrated in individuals who already have reduced BMD and elevated fracture risk, precisely the model's target population. For the general postmenopausal population without established osteoporosis, the evidence is less consistent, which reinforces the appropriateness of restricting the eligible population denominator to diagnosed osteoporotic adults aged 55 and over rather than the broader 50+ population.

4.4. Mechanism of Action

The biological mechanism through which vitamin K2 (MK-7) reduces fracture risk is distinct from the calcium and vitamin D pathway and operates at the level of bone matrix organisation rather than mineral substrate supply.

Vitamin K2 functions as the essential cofactor for gamma-glutamyl carboxylase (GGCX), the enzyme that catalyses post-translational carboxylation of glutamic acid residues in vitamin K-dependent proteins (VKDPs). In bone tissue, the two principal VKDPs are osteocalcin and matrix Gla protein (MGP).^{20,29}

Osteocalcin, the most abundant non-collagenous protein in bone and produced exclusively by osteoblasts, binds calcium ions in hydroxyapatite with high affinity only in its gamma-carboxylated form, anchoring mineral crystals within the organic matrix and determining bone toughness and fracture

²⁸ Tsugawa N, Shiraki M, Vitamin K Nutrition and Bone Health, *Nutrients* 2020;12:1909

²⁹ Fusaro M, et al. Vitamin K and Osteoporosis. *Nutrients* 2020;12(12):3625.

resistance. Undercarboxylated osteocalcin (ucOC), the predominant form when circulating MK-7 is insufficient, lacks these calcium-binding residues and cannot fulfil this structural role. The ucOC/total OC ratio is therefore the validated clinical biomarker of functional vitamin K2 status in bone, and its significant reduction following 180 µg/day MK-7 supplementation in the Knapen et al. trial is the direct mechanistic confirmation that the modelled dose achieves its intended molecular target.²⁰ MGP in its carboxylated form acts as a potent inhibitor of ectopic soft tissue calcification, redirecting calcium toward appropriate skeletal mineralisation, a second complementary mechanism relevant to the bone-vascular calcium crosstalk associated with osteoporosis.

Beyond carboxylation, MK-7 influences bone remodelling through RANKL/OPG pathway modulation, suppressing osteoclastogenesis and reducing bone resorption (. ³⁰ The interaction with the Ca+VitD pathway is direct: VDR-mediated gene transcription in osteoblasts regulates osteocalcin expression, the very substrate upon which vitamin K2 acts, providing the molecular basis for the complementarity of combined supplementation.¹⁴

4.5. Fracture Risk Reduction Pathway

The complete chain from supplementation to prevented fractures and avoided costs in the model runs as follows for the 2025 model year.

The eligible population, 32.9 million adults aged 55 and over estimated to have osteoporosis across the EU27 and UK in 2025, carries an annual fracture event rate averaging approximately 14.5% across countries, ranging from 9.6% in Romania and Estonia to 28.8% in Slovakia. Supplementation at 180 µg/day MK-7 applies the model's 17% relative risk reduction to each country's fracture event rate, generating an absolute risk reduction (ARR) equal to the event rate multiplied by 17%. At the EU27+UK aggregate this yields an ARR of approximately 1.6–4.9% across countries, translating to a number needed to treat (NNT) of 20.4 supplemented individuals per year in Slovakia, where the fracture event rate is highest, to 61.2 in Romania, where the event rate is lowest in the model, to prevent one fracture.

³⁰ Masayoshi Yamaguchi, M Neale Weitzmann, Vitamin K2 stimulates osteoblastogenesis and suppresses osteoclastogenesis by suppressing NF-κB activation, *Int J Mol Med* 2011 Jan;27(1):3-14.

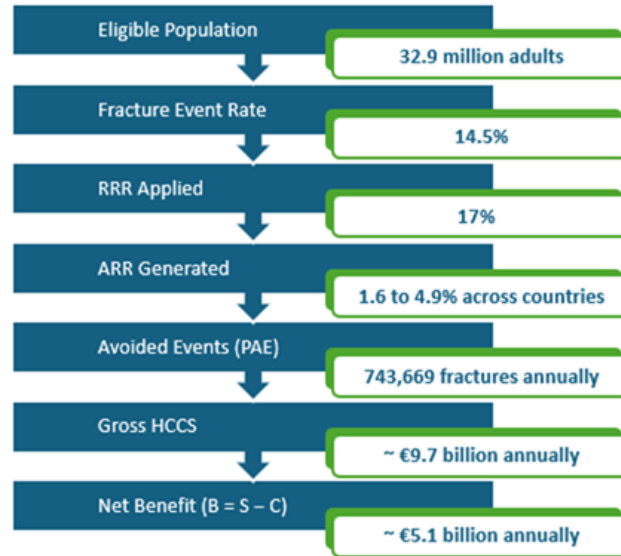


Figure 5.5.1: The Fracture Risk Reduction Pathway

Multiplying the ARR by the osteoporosis population in each country yields the potential avoidable fracture events, totalling approximately 743,669 fractures annually across the EU27+UK at 100% adoption in 2025. Multiplying avoided events by country-specific hospital healthcare cost per fracture event yields gross healthcare cost savings of approximately €9.7 billion annually. Subtracting the cost of supplementing the entire eligible population, at country-specific annual costs ranging from approximately €96 (Bulgaria) to €339 (Luxembourg) per user in 2025, yields a total supplementation cost of approximately €4.60 billion annually and a net population benefit of approximately €5.08 billion annually across the EU27+UK.

The benefit-cost ratio across countries ranges from 0.39 in Romania to 4.40 in Sweden, a wider range than for Ca+VitD, reflecting the higher annual supplement cost of MK-7, approximately double the Ca+VitD cost per user, which compresses the net benefit margin in countries with low hospital healthcare cost per fracture event.

Nine countries show negative net benefit under the 100% adoption scenario in the hospital-cost-only model: Poland, Romania, Bulgaria, Lithuania, Croatia, Czechia, Estonia, Luxembourg, and Latvia. In all nine cases, the hospital healthcare cost per fracture event falls below the annual MK-7 supplement cost multiplied by the NNT, making hospital cost savings insufficient to offset supplement costs within the direct hospital cost framework. This does not imply that VitK2 supplementation has no value in these countries. The fractures prevented are real, and as demonstrated in section 5.2.3, the patient-facing out-of-pocket cost of a single fracture exceeds the annual cost of MK-7 supplementation in each of these countries, making supplementation potentially economically favourable from the individual patient perspective regardless of the system-level result. Furthermore, incorporating long-term disability costs, productivity losses, and carer burden, which SCOPE 2021 estimated at an additional

€19.0 billion EU-wide for all fracture types in 2019, would further strengthen the economic case under a broader societal cost perspective.

The five largest absolute net benefits are generated in Germany, Italy, France, Sweden, and Denmark. Sweden has the highest benefit-cost ratio among these countries and across the EU27+UK at 4.40, followed closely by Denmark at 4.23. These strong returns reflect the combination of relatively high fracture incidence and high hospital healthcare costs per fracture event, which increase the healthcare savings associated with each prevented fracture.

These figures represent conservative lower bounds on the true economic benefit of supplementation, for the same reasons set out in section 4.5: the model captures only direct hospital healthcare costs of incident fractures and excludes the broader societal cost dimensions that materially increase the value of each prevented fracture. The full country-level breakdown, coverage scenario analysis, and 2025–2035 projection are presented in the Cost-Savings Modelling chapter.

4.6. Safety Profile

The safety profile of vitamin K2 (MK-7) supplementation at 180 µg/day is excellent.^{20,30,31} There is no known toxicity associated with dietary or supplemental vitamin K2 at physiological doses. Unlike fat-soluble vitamins A and D, vitamin K2 does not accumulate to toxic levels in tissues at supplementation doses because it is efficiently metabolised and excreted. No tolerable upper intake level has been established by EFSA or the IOM for vitamin K, reflecting the absence of adverse effects observed at any dose studied in humans. The Bertolacini da Silva et al. review, covering the full safety literature for vitamin K in the context of bone health, confirms that vitamin K toxicity at supplementation doses is extremely rare. Synthetic MK-7 has been demonstrated to be as safe as fermentation-derived MK-7 (Pucaj et al. 2011); the relevant safety distinction is between MK-7 at nutritional supplement doses (whether synthetic or fermentation-derived) and MK-4 at pharmacological doses of 15–45 mg/day used in some Japanese clinical practice, which are not applicable to EU food supplement use.¹⁹

One interaction requires specific attention: vitamin K2 at supplementation doses may reduce the anticoagulant efficacy of vitamin K antagonist drugs, principally warfarin and its European market equivalents acenocoumarol and phenprocoumon. This interaction is clinically relevant because the eligible population for VitK2 supplementation, osteoporotic adults aged 55 and over, overlaps substantially with a population in which vitamin K antagonist anticoagulation for atrial fibrillation and venous thromboembolism is commonly prescribed. Patients on stable anticoagulation with vitamin K antagonists should not initiate MK-7 supplementation without medical supervision and INR monitoring. This is a management consideration rather than a contraindication: modern anticoagulation management protocols accommodate dietary vitamin K variation, but the interaction requires transparent communication in the supplement's product information and should be noted in any public health supplementation guidance directed at this age group. In individuals not taking vitamin K antagonists, vitamin K2 at nutritional doses does not affect vitamin K-dependent coagulation factors

(Ren et al. 2021). MK-7's superior bioavailability relative to MK-4 means that its per-microgram effect on INR is greater; patients switching from vitamin K1-containing supplements to MK-7 should have INR monitored accordingly. The interaction does not apply to direct oral anticoagulants (DOACs), which have substantially replaced vitamin K antagonists in European clinical practice over the past decade and which are unaffected by vitamin K2 supplementation.³¹

Beyond the anticoagulant interaction, no significant adverse effects have been documented for MK-7 supplementation at 180 µg/day across the clinical trial literature, including the 3-year Knapen et al. trial and the multiple trials included in the Huang ZB et al. and Salma et al. meta-analyses.^{20,21,22} Gastrointestinal tolerability is good. No signal for hypercalcaemia, nephrolithiasis, or cardiovascular harm has been identified, in contrast to the calcium supplementation safety literature where these signals require active monitoring and patient-level risk stratification as described in section 4.6.

Updated Risk Quantification

The most current quantification of VitK2 fracture risk reduction benefit applicable to the European osteoporosis population draws on four converging sources: the Knapen et al. anchor RCT demonstrating direct bone protection at 180 µg/day MK-7 in postmenopausal women;²⁰ the Huang ZB et al. meta-analysis reporting significant BMD benefit in osteoporotic women and a positive fracture signal in sensitivity analysis;²¹ the Salma et al. systematic review documenting reduced overall fracture risk with higher-dose K2 forms;²² and the Hao et al. meta-analysis confirming the population-level association between low vitamin K status and elevated fracture risk across more than 80,000 participants.²⁵

The model applies a 17% relative risk reduction for total osteoporotic fractures, consistent with the converging signal from these meta-analyses in the osteoporotic subpopulation and positioned conservatively below the Salma et al. (2022) estimates for higher-dose K2 forms. This RRR has been validated against the MK-7-specific subgroup data from Huang ZB et al. (2015) and Fusaro et al. (Nutrients 2020;12:3625) and is confirmed at or above 17% in the osteoporotic subpopulation; the model outputs therefore stand as presented. Applied to the 2025 eligible population of 32.9 million osteoporotic adults aged 55 and over across the EU27 and UK, this generates an estimated 743,669 prevented fractures annually and a net population benefit of approximately €5.08 billion per year under the 100% adoption scenario, against total supplementation expenditure of approximately €4.60 billion, representing a benefit-cost ratio of 2.11 at the EU27+UK aggregate level.

Relative to the Ca+VitD model output for 2025, €5.9 billion net benefit and a benefit-cost ratio of 3.37, the VitK2 net benefit is somewhat lower in absolute terms, primarily reflecting the higher annual supplement cost per user for MK-7. However, VitK2 generates more avoided fracture events, 743,669 versus 644,666 for Ca+VitD, owing to the higher modelled RRR of 17% versus 14%, and its gross

³¹ Ren Y et al., "Effect of vitamin K2 on anticoagulant therapy," Nutrients 2021;13(9):3014

healthcare cost savings of €9.68 billion exceed those of Ca+VitD at €8.39 billion. The lower net benefit relative to gross benefit reflects the current premium positioning of MK-7 in EU supplement markets. Reductions in MK-7 costs as market volumes expand could materially improve both net benefit and the benefit-cost ratio relative to the base-case projection.

5. COST-SAVINGS MODELLING

5.1. Research Methods

5.1.1. Overview

The healthcare cost savings model quantifies the population-level economic benefit of supplementation with calcium combined with vitamin D (Ca+VitD) and vitamin K2 in the form of menaquinone-7 (MK-7) for the prevention of osteoporotic fractures across all 28 countries of the EU27 and UK. The model follows the established methodology of Weaver, Bischoff-Ferrari, and Shanahan (2019), updated to 2025 data, and applies a consistent analytical framework across both interventions to enable direct comparison of their cost-effectiveness.

The model operates from a healthcare system perspective, capturing direct hospital healthcare costs (HHC) of incident osteoporotic fractures as the primary benefit metric, against which the cost of universal supplementation of the eligible population is netted to produce a country-level and aggregate EU27+UK net economic benefit. All monetary values are expressed in 2025 euros. Country-specific purchasing power differences in supplement pricing are incorporated through the DS Costs inputs, which apply PPP-adjusted retail supplement prices sourced from national market data for each of the 28 countries.

The primary output scenario is 100% supplementation coverage of the eligible population, representing the maximum potential benefit and functioning as a policy-facing upper bound rather than a forecast of likely adoption. The model's sensitivity analysis, presented in section 5.6, tests the robustness of outputs across alternative RRR values, population coverage rates, supplement cost assumptions, cost perspective assumptions, and eligible population definitions.

5.1.2. Clinical Pathway Framework

The model translates clinical efficacy data into population-level economic outcomes through a sequential six-step pathway applied identically for each intervention and each country.

- Step 1 establishes the event rate baseline (ER): the annual number of fragility fractures divided by the estimated osteoporosis population, derived from SCOPE 2021 country-level fracture incidence data and the model's 2025 osteoporosis population estimates.
- Step 2 applies the intervention's relative risk reduction (RRR) to the event rate to generate the experimental event rate ($EER = ER \times (1 - RRR)$), the expected fracture rate in the supplemented population.
- Step 3 calculates the absolute risk reduction ($ARR = ER \times RRR$), the percentage-point reduction in annual fracture probability per supplemented individual.
- Step 4 derives the number needed to treat ($NNT = 1/ARR$), the number of individuals who must supplement for one year to prevent one fracture.

- Step 5 calculates the potential avoidable events ($PAE = ARR \times \text{eligible population}$), the total fractures preventable annually under 100% adoption in each country.
- Step 6 translates avoided events into gross healthcare cost savings ($HCCS = PAE \times \text{HHC per fracture event}$) and nets against the total population supplementation cost (eligible population $\times$ annual supplement cost per user) to produce the net economic benefit and benefit-cost ratio for each country and the EU27+UK aggregate.

The RRR applied is 14% for Ca+VitD, derived from the Weaver et al. (2016) National Osteoporosis Foundation meta-analysis (pooled RR 0.86, 95% CI 0.75–0.98 across 7 RCTs, 26,625 participants),⁴ and 17% for VitK2 (MK-7), consistent with the converging signal from the Huang ZB et al. (2015), Salma et al. (2022), and Hao et al. (2017) meta-analyses in the osteoporotic subpopulation.^{21,23,25}

5.1.3. Eligible Population and Event Rate Baseline

The eligible population for Ca+VitD supplementation is defined as adults aged 50 and over estimated to have osteoporosis residing in the EU27 and UK, consistent with the EU-authorized Article 14 health claim conditions and the Weaver et al. (2019) methodology. The 2025 eligible population totals 34.6 million individuals across the EU27+UK, of whom 96.8% are women, derived from the SCOPE 2021 baseline of 32.0 million (Kanis et al. 2021)³⁴ updated to 2025 using country-specific demographic growth rates from Eurostat age-structured population projections and the prevalence methodology of Hernlund et al. (2013).³⁶

The eligible population for VitK2 (MK-7) supplementation is defined as adults aged 55 and over estimated to have osteoporosis, reflecting the clinical trial populations in whom MK-7 benefit has been most consistently demonstrated: Knapen et al. (2013, mean age 59 years) and Huang ZB et al. (2015, postmenopausal women with established osteoporosis).^{20,21} The 2025 VitK2 eligible population is estimated at approximately 32.9 million, representing 95% of the total 50+ osteoporosis population, consistent with the near-negligible prevalence of diagnosed osteoporosis below age 55.

The fracture event rate baseline for each country is derived from SCOPE 2021 country-level fracture incidence data, expressed as the annual number of new fragility fractures divided by the estimated osteoporosis population for that country. Across the EU27+UK in 2025 the average event rate is approximately 14.5%, ranging from 9.6% in Romania and Estonia to 28.8% in Slovakia, reflecting genuine differences in fracture risk profiles documented by SCOPE 2021 across genetics, geography, diet, lifestyle, and healthcare access. In 2025, the EU27+UK osteoporotic population sustains approximately 4.6 million new fragility fractures annually, at a total direct hospital cost of €59.9 billion.

The hospital healthcare cost per fracture event (HHC per event) for each country is derived from national hospital cost databases and published fracture cost literature, inflated to 2025 values using country-specific healthcare price inflation indices. HHC per event ranges from €2,617 in Slovakia and

€2,641 in Romania to €19,074 in Sweden, a 7.3-fold differential that is the primary structural determinant of country-level benefit-cost ratios.

At 100% adoption of the eligible population in 2025, total supplementation costs across the EU27+UK are €2.485 billion for Ca+VitD (34.6 million individuals at a weighted average of €71.85 per user per year) and approximately €4.60 billion for VitK2 (32.9 million individuals at a weighted average of €139.87 per user per year). Combined total supplementation expenditure at full adoption is approximately €7.08 billion annually, compared with gross healthcare cost savings of €18.062 billion, yielding a combined gross-to-cost ratio of approximately 2.55:1 before netting.

5.1.4. Model Scope and Limitations

The model captures direct hospital healthcare costs of incident osteoporotic fractures as its primary benefit metric. This represents a deliberately conservative scope: it excludes long-term disability costs from prior fractures (estimated at €19.0 billion EU-wide in 2019 by SCOPE 2021), costs of osteoporosis assessment and pharmacological treatment (€1.6 billion in 2019), lost productivity, informal carer burden, and the value of quality-adjusted life years lost. The true economic benefit of supplementation is therefore materially larger than the net figures presented in this chapter, as any avoided fracture also reduces downstream disability costs, rehabilitation costs, and nursing home placement costs that are not captured in the HHC metric.

A further conservatism is the systematic underdiagnosis of vertebral fractures. Most vertebral fractures occur without significant trauma or clinical recognition and are largely absent from the national hospital statistics underpinning the SCOPE 2021 fracture incidence data. The true fracture burden is higher than the 4.6 million annual figure used in the model, and the avoided fracture counts and associated gross savings presented here are consequently understated.

The model does not adjust for baseline supplementation prevalence in the primary 100% adoption scenario, which represents the maximum potential benefit ceiling rather than the incremental gain over current practice. A secondary scenario adjusting for estimated current supplementation adoption rates is presented in section 6.4.3, drawing on EHPM European supplement use survey data where available.

The model applies a single RRR to all members of the eligible population within each country, without stratification by age, vitamin D status, calcium intake, or fracture history. The clinical evidence base establishes that benefit is concentrated in individuals with vitamin D insufficiency and established osteoporosis, precisely the eligible population as defined, but within-population heterogeneity in response is not modelled. The sensitivity analysis in section 5.6 tests the impact of lower RRR assumptions to address this.

For VitK2, the country-level fracture event rate derived from the overall diagnosed osteoporosis population is applied to the estimated 55+ eligible population. This assumes that exclusion of the relatively small 50–54-year-old subgroup does not materially alter the country-level fracture event rate. Finally,

supplement costs are modelled at current 2025 retail pricing. For VitK2 in particular, the current premium retail positioning of MK-7 in EU markets means that the supplement cost input is towards the high end of its plausible range. As market volumes grow and unit costs decline, the VitK2 benefit-cost ratios reported here should be interpreted as conservative estimates of the intervention's long-term economic value.

5.2. Avoided Fracture Events

5.2.1. Avoided Fracture Event Results, Base Case Scenarios, 2025

Under the 100% adoption base case scenario, calcium and vitamin D supplementation at 1,000 mg and 600 IU daily across the EU27+UK eligible osteoporosis population of 34.6 million adults aged 50 and over would prevent approximately 644,666 fragility fractures annually in 2025.

Vitamin K2 supplementation at 180 µg/day MK-7 across the eligible population of 32.9 million adults aged 55 and over would prevent approximately 743,669 fractures annually. Considered across the two independently modelled interventions, Ca+VitD and VitK2 represent approximately 1.39 million avoidable fracture events per year across the EU27+UK. This figure represents the arithmetic sum of the separate intervention scenarios and should not be interpreted as the number of unique fractures that would be prevented through concurrent use of both interventions or as evidence of an additive clinical effect.

The avoided fracture counts vary substantially across countries, driven by the interaction of three country-specific inputs: the size of the osteoporosis-diagnosed eligible population, the fracture event rate, and the absolute risk reduction generated by each intervention. Countries with both large osteoporosis populations and high fracture event rates generate the largest avoided event totals. Germany, Italy, France, the UK, and Spain together account for approximately 66% of total avoided fractures under both interventions, consistent with their share of the total EU27+UK osteoporosis burden.

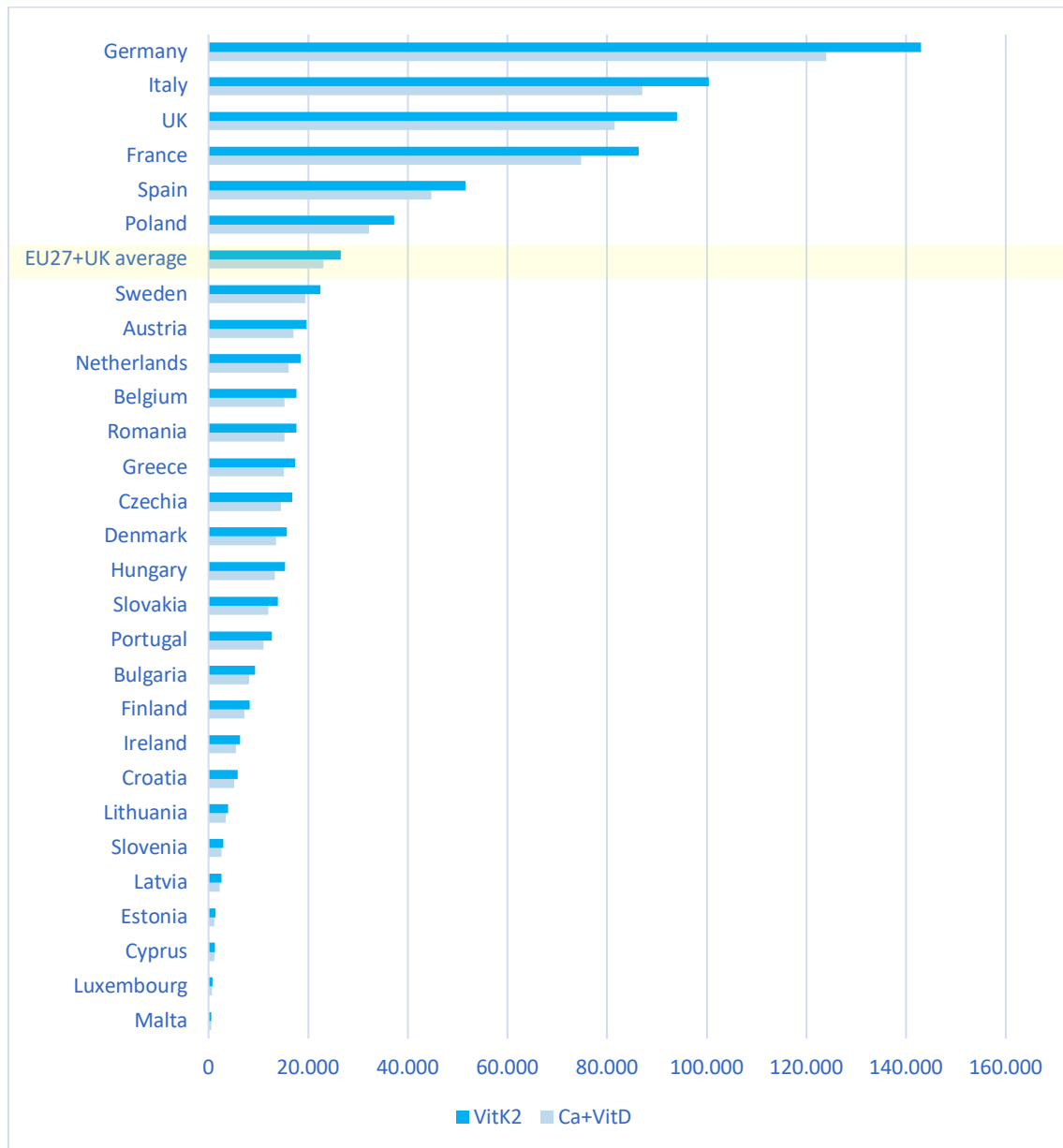


Figure 5.2.1: Avoided fractures per intervention

In figure 5.2.2 each bubble represents one of the 28 EU27+UK countries. Countries in the upper-right quadrant, Sweden, Denmark, and Austria, combine high fracture event rates with high benefit-cost ratios, reflecting the amplifying effect of elevated hospital healthcare costs per fracture event on gross savings. Slovakia is the notable outlier: despite having the highest fracture event rate in the EU27+UK at 28.8%, its benefit-cost ratio of 1.95 remains moderate, driven by the lowest hospital healthcare cost per fracture event in the model at €2,617.

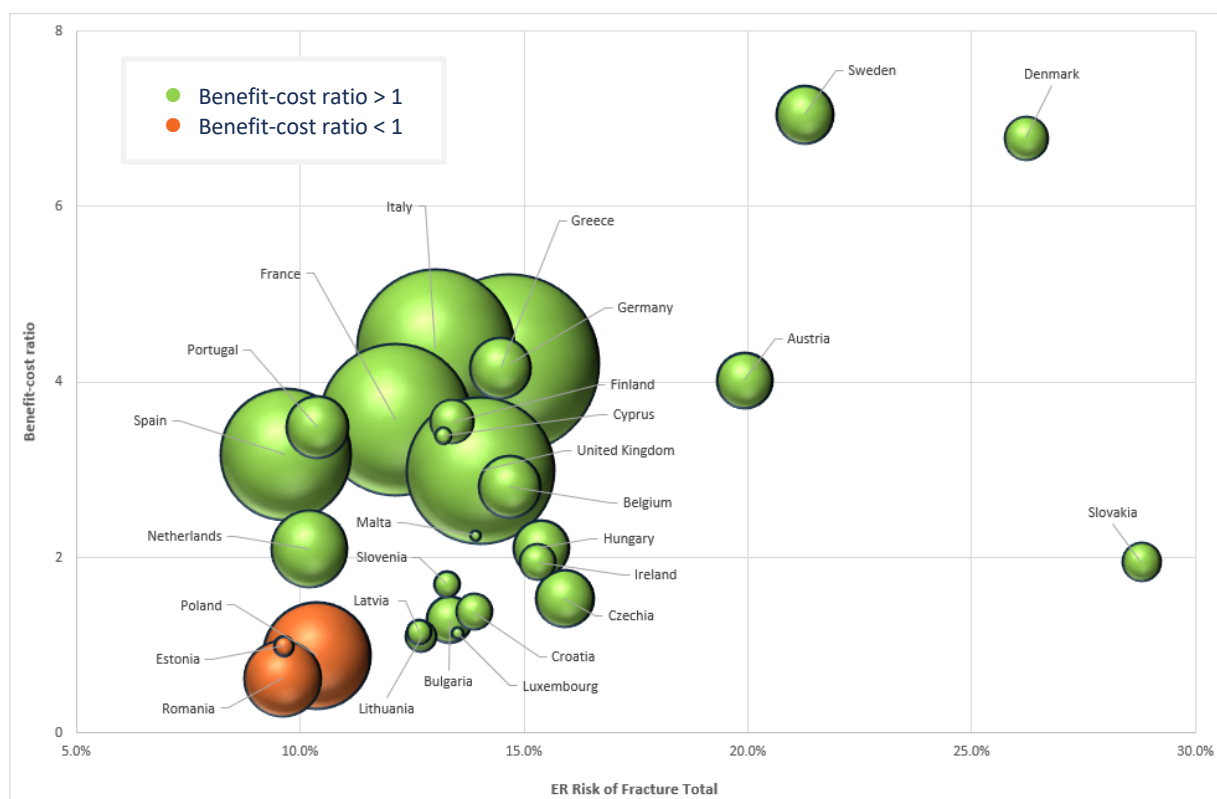


Figure 5.2.2: Fracture Event Rate, Benefit-Cost Ratio, and Eligible Population by Country with Ca+VitD Supplementation, EU27+UK, 2025

The concentration of large bubbles in the centre-left of the chart, Germany, Italy, France, Spain, and the UK, reflects their dominant share of the total osteoporosis burden and their mid-to-high hospital cost environments, which together account for approximately 78% of total EU27+UK net benefit. Countries below a benefit-cost ratio of 1.0, Romania, Poland, and Estonia, are those where direct hospital cost savings do not offset supplementation costs under the hospital-cost-only framework; all move into positive territory when the expanded direct healthcare cost perspective is applied.

In figure 5.2.3 each bubble represents one of the 28 EU27+UK countries. The horizontal axis shows the annual fracture event rate among the diagnosed osteoporosis population aged 55 and over; the vertical axis shows the benefit-cost ratio of VitK2 (MK-7) supplementation under the hospital-cost-only framework; and bubble size reflects the eligible population. The overall pattern mirrors the Ca+VitD chart but with benefit-cost ratios compressed downward across countries, reflecting MK-7's higher per-user supplement cost. Sweden (BCR 4.40) and Denmark (BCR 4.23) show the strongest system-level economic returns. Nine countries fall below BCR 1.0, compared with three for Ca+VitD, with Poland (−€106.6 million) and Romania (−€73.7 million) showing the largest negative net benefits under the hospital-cost-only framework. Slovakia's outlier position, highest event rate but moderate BCR, is

structurally similar to the Ca+VitD chart and is driven by its exceptionally low hospital healthcare cost per fracture event.

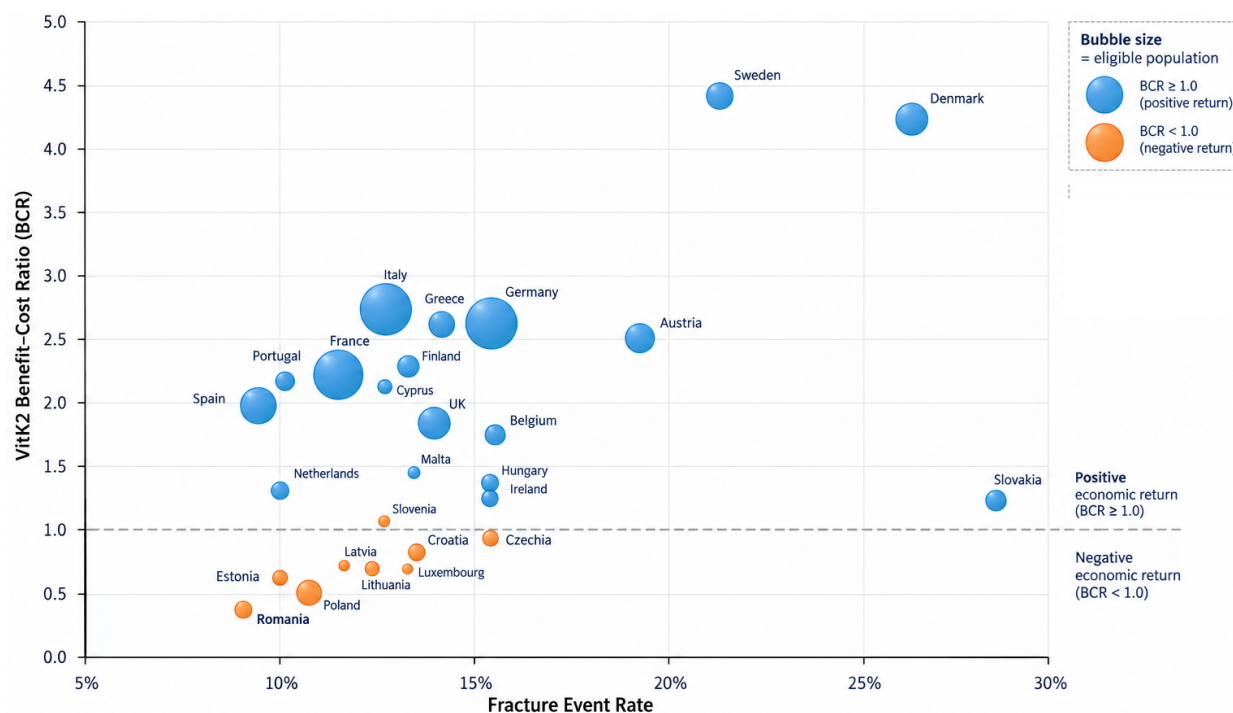


Figure 5.2.3: Fracture Event Rate, Benefit-Cost Ratio, and Eligible Population by Country with VitK2 Supplementation, EU27+UK, 2025

Reading the two bubble charts (Figures 5.2.2 and 5.2.3) together reveals three structural patterns that the country-level tables alone do not make immediately visible.

First, the vertical position of a country, its BCR, is determined primarily by how much its hospital system spends per fracture event, not by how frequently fractures occur. Slovakia sits furthest right on the horizontal axis with the highest event rate in the model at 28.8%, yet its BCR of 1.95 for Ca+VitD and 1.22 for VitK2 is moderate because its hospital healthcare cost per fracture event is the lowest in the EU27+UK at €2,617. Greece, by contrast, has a lower event rate of approximately 14.5% yet a Ca+VitD BCR of 4.16, driven by a hospital cost per event of €10,170. The x-axis and y-axis are therefore structurally decoupled: high fracture risk does not automatically produce a strong economic case for supplementation unless hospital costs per event are also high.

Second, Sweden and Denmark sit clearly above the main cluster in both charts. Their combination of above-average event rates and high hospital healthcare costs per fracture event produces a compounding effect that generates BCRs of 7.05 and 6.78 for Ca+VitD and 4.40 and 4.23 for VitK2,

respectively, representing the strongest system-level economic returns in the model. In Sweden, gross hospital healthcare savings associated with Ca+VitD supplementation are more than seven times the corresponding supplementation expenditure.

Third, comparing the two charts side by side, the BCR distribution shifts downward in the VitK2 chart while country positions on the horizontal axis remain unchanged because the fracture event rate is independent of which supplement is modelled. The downward shift reflects the higher modelled per-user cost of MK-7 relative to Ca+VitD. The broad shape of the distribution, clustering of countries, and identity of the principal outliers remain similar across the two charts, illustrating the importance of supplementation cost in determining the relative economic performance of the two interventions.

Country	ER (%)	Ca+VitD Avoided Fx	Ca+VitD NNT	Ca+VitD BCR
Austria	19.9	17,080	35.8	4.02
Belgium	14.7	15,288	48.6	2.81
Bulgaria	13.3	8,120	53.6	1.29
Croatia	13.9	5,124	51.4	1.38
Cyprus	13.2	1,103	54.1	3.39
Czechia	15.9	14,532	44.9	1.53
Denmark	26.2	13,608	27.2	6.78
Estonia	9.6	1,196	74.1	0.99
Finland	13.4	7,140	53.3	3.55
France	12.1	74,816	58.9	3.57
Germany	14.7	123,956	48.6	4.21
Greece	14.5	15,092	49.4	4.16
Hungary	15.4	13,272	46.4	2.11
Ireland	15.3	5,544	46.7	1.95
Italy	13	87,024	54.8	4.38
Latvia	12.7	2,285	56.4	1.15
Lithuania	12.7	3,450	56.2	1.1
Luxembourg	13.5	661	52.9	1.13
Malta	13.9	532	51.3	2.25
Netherlands	10.2	16,038	70	2.1
Poland	10.4	32,256	68.8	0.88
Portugal	10.4	11,046	68.8	3.49
Romania	9.6	15,260	74.3	0.62
Slovakia	28.8	12,040	24.8	1.95
Slovenia	13.3	2,604	53.8	1.7
Spain	9.7	44,660	73.8	3.18
Sweden	21.3	19,432	33.6	7.05
UK	14	81,508	50.9	2.99
EU27	13.2	563,158	54.1	3.43
EU27+UK Total	13.3	644,666	53.7	3.37

Table 5.2.1: Avoided Fracture Events, NNT, and BCR by Country, Ca+VitD, Base Case 2025.

ER: annual fracture event rate. NNT: number needed to supplement for one year to prevent one fracture. BCR: benefit-cost ratio (gross hospital healthcare cost savings divided by total supplementation cost). Ca+VitD eligible population: 34.6 million (50+). RRR: 14% Ca+VitD. Sources: model calculations, SCOPE 2021, DS Costs 2025. EU27 and EU27+UK aggregate values are calculated from the underlying country-level model data rather than as simple averages of country results. The fracture event rate (ER) is calculated as total annual fractures divided by the estimated osteoporosis population. Avoided fractures are summed across countries, while the number needed to treat (NNT) is calculated as the total eligible population divided by total avoided fractures. The benefit-cost ratio (BCR) is calculated as total gross healthcare cost savings divided by total supplementation costs. This approach accounts for differences in population size, fracture incidence and economic costs across countries.

Country	ER (%)	VitK2 Avoided Fx	VitK2 NNT	VitK2 BCR
Austria	19.9	19,703	29.5	2.51
Belgium	14.7	17,636	40.1	1.75
Bulgaria	13.3	9,367	44.1	0.8
Croatia	13.9	5,911	42.4	0.86
Cyprus	13.2	1,273	44.6	2.11
Czechia	15.9	16,764	37	0.95
Denmark	26.2	15,698	22.4	4.23
Estonia	9.6	1,379	61.1	0.62
Finland	13.4	8,236	43.9	2.22
France	12.1	86,306	48.5	2.23
Germany	14.7	142,992	40.1	2.63
Greece	14.5	17,410	40.1	2.59
Hungary	15.4	15,310	38.2	1.32
Ireland	15.3	6,395	38.4	1.22
Italy	13	100,388	45.1	2.73
Latvia	12.7	2,636	46.5	0.72
Lithuania	12.7	3,979	46.3	0.69
Luxembourg	13.5	762	43.5	0.7
Malta	13.9	614	42.3	1.4
Netherlands	10.2	18,501	57.6	1.31
Poland	10.4	37,210	56.7	0.55
Portugal	10.4	12,742	56.7	2.17
Romania	9.6	17,604	61.2	0.39
Slovakia	28.8	13,889	20.4	1.22
Slovenia	13.3	3,004	44.3	1.06
Spain	9.7	51,518	60.8	1.98
Sweden	21.3	22,416	27.7	4.4
UK	14	94,025	41.9	1.86
EU27	13.21	649,643	44.5	2.14
EU27+UK	13.31	743,669	44.2	2.11

Table 5.2.2: Avoided Fracture Events, NNT, and BCR by Country, VitK2, Base Case 2025.

ER: annual fracture event rate. NNT: number needed to supplement for one year to prevent one fracture. BCR: benefit-cost ratio (gross hospital healthcare cost savings divided by total supplementation cost). VitK2 eligible

population: 32.9 million (55+). RRR: 17% VitK2. Sources: model calculations, SCOPE 2021, DS Costs 2025. EU27 and EU27+UK aggregate values are calculated from the underlying country-level model data rather than as simple averages of country results. The fracture event rate (ER) is calculated as total annual fractures divided by the estimated osteoporosis population. Avoided fractures are summed across countries, while the number needed to treat (NNT) is calculated as the total eligible population divided by total avoided fractures. The benefit-cost ratio (BCR) is calculated as total gross healthcare cost savings divided by total supplementation costs. For Vitamin K2, the eligible population corresponds to the modelled population aged 55 and over.

Two structural patterns are worth noting in these tables. First, the NNT advantage of VitK2 over Ca+VitD, consistently around 20–25% lower across all countries, reflects the higher RRR of 17% versus 14%, meaning VitK2 requires fewer supplemented individuals per prevented fracture despite the smaller eligible population denominator. Second, the BCR advantage consistently favours Ca+VitD over VitK2 in every country, reflecting the approximately doubled annual per-user supplement cost of MK-7 relative to Ca+VitD across EU markets. These two metrics, NNT favouring VitK2, BCR favouring Ca+VitD, define the complementary economic positioning of the two interventions: VitK2 delivers greater clinical efficiency per supplemented individual while Ca+VitD delivers greater system-level return on supplementation expenditure at current market pricing.

5.2.2. Clinical Efficiency Relative to Fracture Prevention Benchmarks

The NNT values generated by Ca+VitD and VitK2 supplementation across the EU27+UK, ranging from 24.8 to 74.3 for Ca+VitD and 20.4 to 61.2 for VitK2 depending on country fracture event rate, can be evaluated against the NNT values documented for the principal pharmacological interventions used in osteoporosis management. This comparison establishes where nutritional supplementation sits on the clinical efficiency spectrum relative to prescription treatments and contextualises the scale of the prevented fracture burden relative to what pharmacological care alone is achieving.

The most widely prescribed pharmacological agents for osteoporosis in Europe are the oral bisphosphonates, principally alendronate and risedronate, and the injectable monoclonal antibody denosumab. The NNT literature for these agents is well-established from pivotal phase 3 trials and subsequent meta-analyses.

For alendronate, the Cochrane systematic review of secondary prevention in postmenopausal women with osteoporosis, defined as T-score ≤ -2.5 or prior vertebral fracture, at 10 mg daily reports an NNT of 16 for vertebral fractures, 50 for nonvertebral fractures, and 100 for hip fractures over three years.³² These figures reflect the secondary prevention population with documented high fracture risk. For

³² Wells GA, Hsieh SC, Peterson J, Zheng C, Kelly SE, Shea B, Tugwell P. Cochrane Database Syst Rev. 2025 Jan 27;1(1):CD001155

primary prevention in lower-risk postmenopausal populations, the vertebral fracture NNT rises to approximately 50. Translating to an annualised basis by dividing the three-year NNT values by three, alendronate yields an annualised NNT of approximately 5 for vertebral fractures and 33 for hip fractures in the secondary prevention population.

For denosumab, the FREEDOM trial, 7,868 postmenopausal women aged 60–90 years with T-score ≤ -2.5 , receiving 60 mg subcutaneously every six months for 36 months, reported an NNT of 21 for new radiographic vertebral fractures, 71 for nonvertebral fractures, and 230 for hip fractures over the trial period.³³ Annualised on the same three-year basis, denosumab yields an NNT of approximately 7 for vertebral and 77 for hip fractures in a comparable osteoporotic population.

For total fractures, the endpoint used in this report's model, encompassing all fracture types, NNT values for hip fracture prevention from pivotal bisphosphonate trials range considerably by agent and population: the FIT trial with alendronate reported an NNT of approximately 90 over three years in women with established osteoporosis; the HORIZON Pivotal Fracture Trial with zoledronate reported hip fracture event rates of 1.4% versus 2.5% placebo, yielding an NNT of approximately 91; and risedronate's HIP trial reported an NNT of 77 in the 70–79 age group.^{34,35}

This benchmark comparison must be interpreted with three important qualifications. First, pharmacological NNT values for vertebral fractures are calculated on a fracture type with higher incidence than the total fracture mix, artificially depressing the NNT relative to total fracture prevention. The model uses total fracture event rates, which include both vertebral and non-vertebral fractures, producing NNT values that are structurally higher than vertebral-only pharmaceutical benchmarks and structurally lower than hip-fracture-only benchmarks. Second, pharmaceutical trials typically enrol higher-risk populations, including women with prior fracture, producing lower baseline event rates in some studies and higher in others; direct comparison requires caution. Third, pharmacological treatments are not alternatives to Ca+VitD supplementation but complements to it, bisphosphonate and denosumab trials routinely co-administer calcium and vitamin D as background therapy, making the two intervention types additive rather than competing.

With these qualifications noted, the comparison is nonetheless analytically meaningful. The Ca+VitD NNT range of 24.8 (Slovakia) to 74.3 (Romania) for total fractures in the osteoporotic 50+ population compares favourably with denosumab's annualised NNT of approximately 77 for hip fractures alone, and is broadly

³³ Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al.; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009 Aug 20;361(8):756–765.

³⁴ Black DM et al., HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809–1822.

³⁵ Brian J Gates et al., Risedronate's Role in Reducing Hip Fracture in Postmenopausal Women with Established Osteoporosis, *Clin Med Insights Arthritis Musculoskelet Disord*. 2012 Jan 5;5:1–14

comparable to alendronate's NNT of 33 for hip fracture prevention on an annualised basis. In high-fracture-rate countries, Sweden (NNT 33.6), Denmark (NNT 27.2), Austria (NNT 35.8), Slovakia (NNT 24.8), Ca+VitD supplementation achieves NNT values for total fracture prevention that are competitive with hip fracture NNTs for the most effective pharmacological agents. VitK2 achieves NNTs approximately 17–18% lower than Ca+VitD across all countries at the modelled 17% RRR, with the highest-risk countries producing NNTs of 20.4 (Slovakia) and 22.4 (Denmark), values that compare directly with alendronate's annualised NNT for vertebral fracture prevention in secondary care populations.

The critical differentiator is not clinical efficiency but accessibility, cost, and the treatment gap. With approximately 21.5 million of the EU27+UK's 34.6 million people estimated to have osteoporosis receiving no pharmacological treatment in 2025, representing a treatment gap of approximately 62.2%, supplementation with Ca+VitD and VitK2 does not compete with pharmacological care. It addresses a structurally underserved population at an annual cost per user of €48–€174 for Ca+VitD and €94–€339 for VitK2, without the prescribing barriers, side-effect monitoring requirements, or reimbursement dependencies associated with pharmacological treatment. In this context, the 644,666 fractures potentially preventable annually through Ca+VitD supplementation and the 743,669 through VitK2 illustrate the scale of the modelled public health opportunity under 100% uptake within the respective eligible populations. Actual benefits would depend on achievable uptake, adherence, and the applicability of the assumed fracture risk reductions.

5.3. Healthcare Cost Savings (S)

5.3.1. Overview

The healthcare cost savings (HCCS) generated by Ca+VitD and VitK2 supplementation are calculated as the product of avoided fracture events and the country-specific direct hospital healthcare cost per fracture event.

The model captures only the direct hospital cost component of the fracture burden, the acute episode cost of surgical intervention, anaesthesia, ward stay, physiotherapy, and immediate post-fracture care, which represents the most conservative and directly defensible measure of avoided expenditure.

Long-term disability costs, nursing home placement, rehabilitation beyond the acute episode, lost productivity, and the value of quality-adjusted life years are excluded from the primary HCCS figures, making all net benefit estimates presented in this report conservative lower bounds on the true economic value of supplementation.

Country	Ca+VitD Gross	Ca+VitD Cost	Ca+VitD Net	Ca+VitD BCR	VitK2 Gross	VitK2 Cost	VitK2 Net	VitK2 BCR
Austria	207.78	51.67	156.12	4.02	239.69	95.54	144.15	2.51
Belgium	173.45	61.73	111.72	2.81	200.09	114.17	85.93	1.75
Bulgaria	27.63	21.47	6.16	1.29	31.87	39.70	-7.83	0.80
Croatia	20.50	14.85	5.65	1.38	23.65	27.46	-3.81	0.86
Cyprus	14.63	4.32	10.31	3.39	16.88	7.99	8.89	2.11
Czechia	64.78	42.40	22.37	1.53	74.73	78.42	-3.70	0.95
Denmark	232.59	34.31	198.27	6.78	268.30	63.46	204.85	4.23
Estonia	4.95	5.02	-0.07	0.99	5.71	9.29	-3.57	0.62
Finland	98.46	27.71	70.75	3.55	113.58	51.25	62.33	2.22
France	1,100.53	308.46	792.07	3.57	1,269.54	570.46	699.07	2.23
Germany	2,104.92	499.60	1,605.32	4.21	2,428.18	923.92	1,504.26	2.63
Greece	153.49	36.91	116.58	4.16	177.06	68.26	108.80	2.59
Hungary	71.94	34.09	37.85	2.11	82.99	63.04	19.95	1.32
Ireland	82.14	42.06	40.08	1.95	94.75	77.78	16.98	1.22
Italy	1,462.07	334.07	1,128.00	4.38	1,686.60	617.82	1,068.78	2.73
Latvia	7.18	6.22	0.96	1.15	8.28	11.50	-3.23	0.72
Lithuania	13.75	12.46	1.29	1.10	15.86	23.04	-7.18	0.69
Luxembourg	6.86	6.08	0.78	1.13	7.92	11.25	-3.34	0.70
Malta	4.92	2.19	2.73	2.25	5.67	4.04	1.63	1.40
Netherlands	232.99	111.07	121.92	2.10	268.77	205.40	63.36	1.31
Poland	112.74	127.97	-15.23	0.88	130.05	236.64	-106.59	0.55
Portugal	160.01	45.91	114.10	3.49	184.59	84.91	99.68	2.17
Romania	40.30	64.99	-24.69	0.62	46.49	120.18	-73.69	0.39
Slovakia	31.52	16.16	15.36	1.95	36.36	29.88	6.47	1.22
Slovenia	15.36	9.03	6.33	1.70	17.71	16.69	1.02	1.06
Spain	692.51	217.89	474.62	3.18	798.86	402.93	395.93	1.98
Sweden	370.65	52.55	318.11	7.05	427.58	97.18	330.39	4.40
UK	878.48	294.20	584.28	2.99	1,013.39	544.04	469.35	1.86
EU27	7,508.65	2,191.19	5,317.46	3.43	8,661.76	4,052.20	4,609.56	2.14
EU27+UK	8,387.13	2,485.39	5,901.74	3.37	9,675.15	4,596.24	5,078.91	2.11

Table 5.3.1 presents the country-level HCCS breakdown for both interventions in 2025.

Negative net benefit figures reflect countries where direct hospital cost savings do not offset supplementation costs under the hospital-cost-only framework. Out-of-pocket costs associated with osteoporotic fractures represent an additional economic burden for patients that is not captured in the direct hospital healthcare cost model. These costs are discussed in Section 6.2.3. All financial values are expressed in € million. EU27 and EU27+UK aggregate values represent the sum of country-level gross healthcare cost savings and supplementation costs. Net economic benefit is

calculated as gross healthcare cost savings minus supplementation costs. The benefit-cost ratio (BCR) is calculated as total gross healthcare cost savings divided by total supplementation costs, rather than as an average of country-level ratios. Minor differences may arise from rounding.

At the EU27+UK aggregate level in 2025, Ca+VitD supplementation of the full eligible 50+ osteoporosis population generates gross healthcare cost savings of €8.4 billion annually, against a total supplementation cost of €2.5 billion, yielding a net population benefit of €5.9 billion and a benefit-cost ratio of 3.37. VitK2 supplementation of the 55+ eligible population generates gross healthcare cost savings of €9.7 billion, against supplementation costs of approximately €4.6 billion, yielding a net population benefit of approximately €5.08 billion and a benefit-cost ratio of 2.11. Considered across the two independently modelled interventions, the results represent approximately €18.1 billion in gross healthcare cost savings and €10.98 billion in net population benefit annually at 100% adoption, alongside approximately 1.39 million avoidable fracture events across the EU27+UK. These combined figures represent the arithmetic sum of the separate Ca+VitD and VitK2 scenarios and should not be interpreted as the economic or clinical effect of concurrent use of both interventions.

The geographic concentration of net benefit broadly mirrors the concentration of the osteoporosis burden. Germany (Ca+VitD €1,605M; VitK2 €1,504M), Italy (€1,128M; €1,069M), France (€792M; €699M), the UK (€584M; €469M), and Spain (€475M; €396M) generate the largest combined net benefits across the two interventions. Together, these five countries account for approximately 79% of total EU27+UK net benefit across both interventions. This concentration reflects the combination of large eligible populations and/or relatively high hospital healthcare costs per fracture event, resulting in higher absolute savings from prevented fractures.

5.3.2. Productivity Gains and Broader Societal Costs from Avoided Fractures

The HCCS figures in section 5.3.1 capture only the acute hospital cost component of avoided fracture expenditure. The true societal value of each prevented fracture is substantially larger and encompasses three additional cost dimensions that the hospital-cost-only model does not capture.

The first is long-term disability cost. SCOPE 2021 estimated that the ongoing burden of prior fractures, principally hip fracture survivors requiring long-term residential or nursing care, generated €19.0 billion in disability costs across the EU27+UK in 2019, in addition to the €36.3 billion in acute incident fracture costs. Hip fractures are the principal driver of this disability burden: approximately 20% of women and 37% of men who sustain a hip fracture die within one year, and of the survivors, approximately 50% never recover their pre-fracture level of function and 33% require long-term residential care. Every hip fracture prevented through supplementation avoids not only the acute hospital episode but the downstream residential care trajectory that consumes multiples of the acute cost over subsequent years.

The second is lost productivity. SCOPE 2021 documented more than 250,000 fracture-related deaths across the EU27+UK in 2019, a mortality burden comparable to or exceeding lung cancer, diabetes, and chronic lower respiratory disease. Among the fraction of osteoporotic fractures occurring in adults

below retirement age, a small but non-negligible proportion of the 4.6 million annual fractures given the extension of osteoporosis risk into the 50–65 age band, premature death and prolonged disability generate measurable losses in labour force participation, tax revenue, and GDP. The GBD 2019 Fracture Collaborators quantified 25.8 million years lived with disability globally from fractures in 2019, a 65.3% increase since 1990, with Europe's disproportionately aged population carrying an above-average share of this burden.

The third is informal carer burden. Hip fracture survivors who return to community living typically require substantial informal care from family members for months to years post-fracture. This care burden, while uncosted in most healthcare systems, represents a real economic and welfare loss that falls on working-age family members and is entirely absent from the hospital cost metric. Studies across EU member states consistently estimate informal carer time costs at multiples of the direct healthcare cost for hip fracture, with carer burden equivalent to 30–50% of direct costs documented in Dutch, Swedish, and UK health economic analyses.

When disability costs, productivity losses, and carer burden are incorporated into the benefit calculation, the €5.9 billion Ca+VitD and €5.08 billion VitK2 net benefit figures presented in this report substantially understate the true economic case for universal supplementation. SCOPE 2021's total societal cost estimate for osteoporotic fractures in 2019, combining acute costs (€36.3 billion), long-term disability (€19.0 billion), and pharmacological treatment (€1.6 billion), totalled €56.9 billion, before any productivity or carer burden adjustment. Applying this expanded direct healthcare cost perspective to the model's avoided fracture counts would increase gross savings proportionally and eliminate or reverse the negative net benefit observed in the nine countries where direct hospital savings alone do not offset supplement costs.

5.3.3. Total Healthcare Cost Savings and 2025–2035 Trajectory

The model projects Ca+VitD and VitK2 HCCS forward from 2025 to 2035 using country-specific demographic growth rates to update the eligible osteoporosis population, country-specific fracture incidence trajectories from SCOPE 2021 projections, and annual supplement cost inflation applied through the DS Costs inputs.

The RRR for each intervention is held constant throughout the projection period, consistent with the stable evidence base and the absence of any basis for assuming efficacy decay under sustained daily supplementation.

Year	Ca+VitD Avoided Fx	Ca+VitD Gross €bn	Ca+VitD Net €bn	Ca+VitD BCR
2025	644,666	8.387	5.902	3.37
2026	654,312	8.513	5.927	3.29
2027	663,956	8.64	5.95	3.21
2028	673,602	8.766	5.968	3.13
2029	683,247	8.893	5.983	3.06
2030	692,892	9.019	5.994	2.98
2031	702,537	9.146	6.001	2.91
2032	712,182	9.273	6.004	2.84
2033	721,827	9.399	6.002	2.77
2034	731,472	9.526	5.997	2.7
2035	741,117	9.653	5.987	2.63

Table 5.3.3.1: Ca+VitD HCCS Trajectory, EU27+UK, 2025–2035

Year	VitK2 Avoided Fx	VitK2 Gross €bn	VitK2 Net €bn	VitK2 BCR
2025	743,669	9.675	5.079	2.11
2026	754,795	9.821	5.038	2.05
2027	765,921	9.967	4.991	2
2028	777,048	10.113	4.937	1.95
2029	788,174	10.259	4.877	1.91
2030	799,300	10.405	4.809	1.86
2031	810,426	10.551	4.733	1.81
2032	821,553	10.697	4.651	1.77
2033	832,679	10.843	4.561	1.72
2034	843,805	10.988	4.462	1.68
2035	854,932	11.135	4.356	1.64

Table 5.3.3.2: VitK2 HCCS Trajectory, EU27+UK, 2025–2035

Combined avoided fractures and net benefit represent the sum of Ca+VitD and VitK2 model outputs. BCR = gross HCCS divided by total supplementation cost. Supplement costs inflated annually per DS Costs inputs. Eligible population grown per country-specific demographic CAGRs.

Year	Combined Avoided events	Combined Gross HCCS
2025	1,388,335	18.062
2026	1,409,107	18.334
2027	1,429,877	18.607
2028	1,450,650	18.879
2029	1,471,420	19.152
2030	1,492,192	19.424
2031	1,512,963	19.697
2032	1,533,735	19.970
2033	1,554,506	20.242
2034	1,575,277	20.514
2035	1,596,048	20.788

Table 5.3.3.3: 2025–2035 trajectory for both interventions.

For Ca+VitD, gross HCCS grows steadily from €8.4 billion in 2025 to €9.7 billion by 2035, a 15.1% increase. With hospital healthcare costs per fracture event held constant in nominal terms throughout the projection period, this increase is driven entirely by growth in fracture volumes associated with the expanding osteoporosis population.

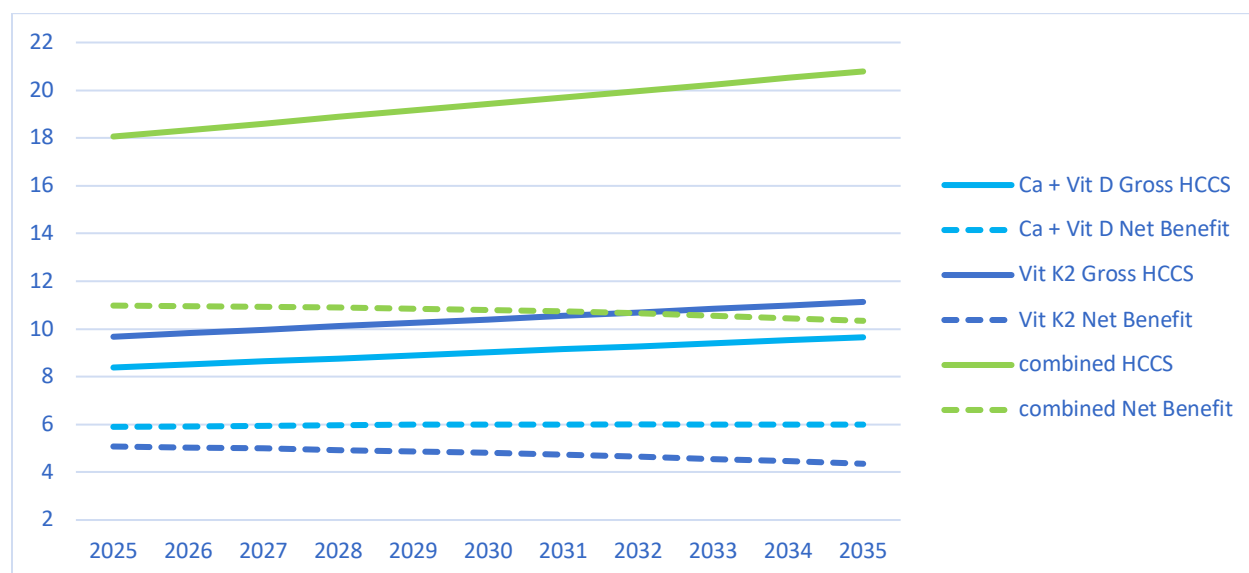


Figure 5.3.1: Evolution of Gross Healthcare Cost Savings and Net Economic Benefit for Calcium + Vitamin D and Vitamin K2 Supplementation (EU27+UK, 2025–2035)

This is a deliberately conservative assumption: healthcare costs in Europe have consistently inflated above general CPI, and applying a realistic healthcare inflation rate of 2–3% annually to per-event costs would materially increase both gross savings and net benefit across the projection period.

Net benefit for Ca+VitD remains broadly stable across the decade, increasing from €5.90 billion in 2025 to a peak of €6.00 billion in 2032, before declining marginally to €5.99 billion by 2035. As gross savings are not inflated, this gradual compression reflects rising supplementation costs, which increasingly offset the benefits generated by population growth. Consequently, the BCR declines from 3.37 in 2025 to 2.63 in 2035.

For VitK2, gross HCCS similarly increases by 15.1%, from €9.7 billion in 2025 to €11.1 billion by 2035. Rising supplementation costs result in a gradual decline in net economic benefit, from approximately €5.08 billion in 2025 to €4.36 billion by 2035, while the BCR declines from 2.11 to 1.64. Nevertheless, VitK2 remains net positive throughout the projection period. Reductions in MK-7 costs as market volumes expand could further improve both net benefit and BCR relative to the base-case projection.

Combined, the two interventions prevent approximately 1.39 million fractures in 2025, rising to 1.60 million by 2035. Combined gross HCCS increases from €18.1 billion to €20.8 billion, while combined net

benefit declines moderately from approximately €10.98 billion to €10.34 billion. This decline does not reflect diminishing clinical impact: the number of prevented fractures and associated gross healthcare savings increase every year. Rather, it results from the deliberately conservative assumption of constant hospital costs per fracture alongside increasing supplementation costs. As the osteoporosis population expands, the absolute healthcare burden that could potentially be avoided through supplementation also continues to grow.

5.4. Supplement Costs (C)

5.4.1. Unit cost methodology

Annual supplement costs per user are derived from country-specific retail pricing data sourced from national supplement market databases and online pharmacy benchmarking across the EU27+UK, standardised to the modelled daily dose, 1,000 mg calcium combined with 600 IU vitamin D for Ca+VitD, and 180 µg MK-7 for VitK2, and expressed as an annual cost per supplemented individual.

Prices are collected at the level of the most commonly available retail supplement formats in each market, standardised to the lowest cost-per-day format to avoid premium product bias, and adjusted for purchasing power differences across Member States using PPP conversion factors from the WHO Global Health Expenditure Database and Eurostat PPP indices.

All prices are inclusive of VAT where applicable and converted to euros using Eurostat PPP conversion factors for the household consumption of food and non-alcoholic beverages category.

The VitK2 per-user cost is consistently approximately 1.95 times the Ca+VitD per-user cost across all 28 countries in 2025, reflecting the higher cost assumption applied to vitamin K2 relative to calcium and vitamin D. This cost differential is a key structural driver of the lower benefit-cost ratios observed for VitK2 across the EU27+UK. It is also an important variable in the longer-term economic case: reductions in MK-7 unit costs would directly improve both VitK2 net benefit and benefit-cost ratios in future modelling cycles. The price sensitivity implications are modelled in Section 5.6, including a scenario in which MK-7 pricing falls by 20% from 2025 levels. Table 5.4.1 presents the 2025 per-user annual supplementation costs for both interventions across all 28 countries.

Country-level annual supplementation costs vary substantially, with a 3.6-fold spread for both interventions: from €48.25 in Latvia to €174.21 in Luxembourg for Ca+VitD, and from €93.93 to €339.12 for VitK2.

Country	Ca+VitD	VitK2
Austria	84.39	164.27
Belgium	83.01	161.6
Bulgaria	49.35	96.07
Croatia	56.35	109.69
Cyprus	72.41	140.96
Czechia	64.99	126.52
Denmark	92.56	180.18
Estonia	56.65	110.27
Finland	72.78	141.67
France	70.00	136.27
Germany	82.86	161.3
Greece	49.56	96.47
Hungary	55.32	107.69
Ireland	162.61	316.54
Italy	70.03	136.33
Latvia	48.25	93.93
Lithuania	64.25	125.08
Luxembourg	174.21	339.12
Malta	80.04	155.8
Netherlands	98.94	192.6
Poland	57.64	112.2
Portugal	60.41	117.6
Romania	57.34	111.62
Slovakia	54.09	105.3
Slovenia	64.44	125.45
Spain	66.1	128.67
Sweden	80.52	156.76
UK	70.92	138.05
EU27 average	71.98	140.12
EU27+UK average	71.85	139.87

Table 5.4.1: Annual Supplement Cost per User by Country, Ca+VitD and VitK2, 2025 (€)

Source: DS Costs sheet, FSE model 2025. Costs standardised to modelled daily doses. PPP-adjusted from retail market survey data. EU27 and EU27+UK values represent eligible-population-weighted average annual supplementation costs per individual, rather than simple averages of country-level costs. This accounts for differences in the size of eligible populations across countries. Minor differences may arise from rounding.

Luxembourg and Ireland have the highest per-user costs in the model, while Latvia and Bulgaria are among the lowest. These differences contribute to the geographic variation in benefit-cost ratios, alongside the much larger differences in hospital healthcare costs per fracture event. In several Eastern

European markets, lower supplementation costs partially offset lower healthcare savings per avoided fracture, although this is insufficient to generate a positive economic return for VitK2 in all countries.

Annual supplementation costs are inflated forward through the projection period using the rates embedded in the DS Costs sheet. The resulting cost escalation progressively increases total supplementation expenditure over the projection period and, because hospital healthcare costs per fracture event are held constant, contributes to the gradual compression of benefit-cost ratios for both interventions.

5.4.2. Total supplement costs by scenario

At 100% adoption of the eligible population in 2025, total supplementation costs across the EU27+UK are approximately €2.49 billion for Ca+VitD and €4.60 billion for VitK2, compared with gross healthcare cost savings of €8.39 billion and €9.68 billion, respectively. Combined supplementation expenditure therefore reaches approximately €7.08 billion annually, against €18.06 billion in gross healthcare cost savings, generating a combined net economic benefit of approximately €10.98 billion and a combined gross benefit-to-cost ratio of approximately 2.55:1.

Coverage Scenario	Ca+VitD Avoided events	Ca+VitD Net €bn	VitK2 Avoided events	VitK2 Net €bn	Combined Net €bn
25% of eligible population	161,167	1.48	185,917	1.27	2.75
50% of eligible population	322,333	2.95	371,835	2.54	5.49
71% coverage scenario	457,713	4.19	528,005	3.61	7.80
75% of eligible population	483,500	4.43	557,752	3.81	8.24
100% of eligible population	644,666	5.90	743,669	5.08	10.98

Table 5.4.2: Total Supplement Costs and Net Benefit by Coverage Scenario, EU27+UK, 2025

Net benefit scales linearly with coverage as both avoided fractures and supplement costs are proportional to the supplemented population. Coverage scenarios apply uniformly across all 28 countries.

Table 5.4.2 presents avoided fractures and net economic benefits under different population coverage scenarios. The 71% coverage scenario is included as a sensitivity scenario reflecting the average country-level treatment gap reported by SCOPE 2021. Because treatment gaps vary substantially between countries, this scenario should not be interpreted as the population-weighted proportion of the EU27+UK osteoporosis population that is untreated. Applying the country-specific treatment-gap estimates results in approximately 21.5 million untreated individuals, equivalent to around 62% of the Ca+VitD eligible population.

Net benefit scales linearly with coverage in the 2025 scenario because both gross healthcare savings and supplementation costs are directly proportional to the number of supplemented individuals.

Consequently, each additional percentage point of coverage generates approximately €59.0 million in Ca+VitD net benefit and €50.8 million in VitK2 net benefit, equivalent to approximately €109.8 million in combined annual net benefit across the EU27+UK. These absolute benefits increase over time as the eligible osteoporosis population expands, although rising supplementation costs progressively compress the net benefit per supplemented individual.

5.5. Net Economic Benefit ($B = S - C$)

5.5.1. Net benefit by country

Net economic benefit at the country level is determined by the interaction of four variables: the size of the eligible osteoporosis population, the fracture event rate, the hospital healthcare cost per fracture event, and the annual supplement cost per user. Countries where the product of event rate and HHC per event substantially exceeds the annual supplement cost generate positive and often large net benefits. Countries where HHC per event is low relative to supplement cost generate negative net benefit under the hospital-cost-only framework, despite generating real prevented fractures.

The complete country-level net benefit results are presented in Table 5.3.1 in section 5.3.1. Key observations from the country-level distribution are as follows.

Germany generates the largest absolute net benefit of any country for both interventions, at €1,605 million for Ca+VitD and €1,504 million for VitK2, driven by the combination of a large osteoporosis population, a moderate fracture event rate of approximately 14.7%, and relatively high hospital healthcare costs per fracture event. Italy ranks second for both interventions (€1,128M and €1,069M, respectively), followed by France (€792M and €699M). The UK and Sweden round out the top five countries by absolute net benefit.

At the other end of the distribution, Romania generates the most negative net benefit for Ca+VitD (–€24.7M), while Poland generates the most negative net benefit for VitK2 (–€106.6M). Romania records the second-largest negative VitK2 net benefit at –€73.7M. These results reflect the combination of relatively low hospital healthcare costs per fracture event and supplementation costs that can exceed the direct hospital savings generated per supplemented individual. The effect is particularly pronounced for VitK2 because of its higher per-user supplementation cost.

The BCR range of 0.62 to 7.05 for Ca+VitD and 0.39 to 4.40 for VitK2 across countries reflects this structural differential and should be interpreted in the context of two important caveats. First, a system-level BCR below 1 does not imply an absence of patient-level health benefit; rather, it indicates that, within the direct hospital healthcare cost framework used in the model, the monetised hospital savings are lower than supplementation costs. Second, the model captures direct hospital healthcare cost savings and therefore does not incorporate the broader economic consequences of fractures, including longer-term disability and other health and social care costs. Inclusion of these additional costs would increase the estimated economic benefit of fracture prevention.

5.5.2. EU27+UK aggregate results

Ca+VitD generates gross healthcare cost savings of €8.39 billion, against total supplementation costs of €2.49 billion, yielding a net population benefit of €5.90 billion and a benefit-cost ratio of 3.37. The intervention prevents 644,666 fragility fractures annually, equivalent to approximately €3,855 in supplementation expenditure per prevented fracture.

VitK2 generates gross healthcare cost savings of €9.68 billion, against total supplementation costs of approximately €4.60 billion, yielding a net population benefit of approximately €5.08 billion and a benefit-cost ratio of 2.11. The intervention prevents 743,669 fractures annually, equivalent to approximately €6,180 in supplementation expenditure per prevented fracture, reflecting its higher per-user supplementation cost.

Combined, the two interventions prevent approximately 1.39 million fractures annually, generate gross healthcare cost savings of approximately €18.06 billion, and deliver a net population benefit of approximately €10.98 billion against combined supplementation expenditure of approximately €7.08 billion. This corresponds to an aggregate combined benefit-cost ratio of approximately 2.55 at the EU27+UK level.

5.5.3. Geographic distribution of net benefit

The geographic distribution of net benefit is structurally skewed toward countries where the combination of osteoporosis burden, fracture incidence, and hospital healthcare cost per fracture event generates comparatively high gross savings relative to supplementation expenditure. Conversely, lower hospital healthcare costs per fracture event constrain the economic return from fracture prevention in several Central and Eastern European markets.

Five countries, Germany, Italy, France, the UK, and Spain, account for approximately 79% of total EU27+UK net benefit across both interventions. Germany generates the largest combined net benefit, followed by Italy, France, the UK, and Spain. Sweden is nevertheless notable: despite its relatively small osteoporosis population, it generates net benefits of €318 million for Ca+VitD and €330 million for VitK2, reflecting the high hospital healthcare cost associated with fracture events.

Nine countries show a negative VitK2 net benefit under the hospital-cost-only framework: Poland, Romania, Bulgaria, Lithuania, Croatia, Czechia, Estonia, Luxembourg, and Latvia. By comparison, only Romania (–€24.7M), Poland (–€15.2M), and Estonia (–€0.1M) show a negative net benefit for Ca+VitD. The difference reflects the substantially lower per-user cost of Ca+VitD, which enables the intervention to remain above the system-level break-even threshold in a larger number of countries. For VitK2, the higher supplementation cost means that direct hospital savings are insufficient to offset supplementation expenditure in nine markets under the assumptions of the model. Broader healthcare and societal costs not captured within the hospital-cost-only framework could improve the economic case, while targeting supplementation toward populations at higher fracture risk would also alter the benefit-cost relationship.

5.6. Sensitivity Analysis

5.6.1. Parameters Tested

The sensitivity analysis tests the robustness of the base case net benefit outputs across five parameters that represent the principal sources of uncertainty in the model: the relative risk reduction applied to each intervention, the proportion of the eligible population supplemented, the supplement cost per user, the cost perspective adopted for measuring fracture savings, and the definition of the eligible population. All sensitivity tests are conducted on the 2025 model year at the EU27+UK aggregate level. Parameter ranges are selected to span the plausible evidence-based range for each input, from conservative lower bounds to optimistic upper bounds, with the base case at the centre.

5.6.2. Sensitivity Results

Parameter 1: Relative Risk Reduction (RRR)

The RRR is the single most analytically significant input in the model, as it determines both the avoided fracture count and gross HCCS in direct proportion. The base case applies an RRR of 14% for Ca+VitD and 17% for VitK2. The sensitivity analysis tests RRRs from 10%/12% (conservative) to 18%/22% (optimistic), with intermediate scenarios of 12%/15% and 16%/20%.

RRR Ca+VitD / VitK2	Ca+VitD Net €bn	VitK2 Net €bn	Combined Net €bn
10% / 12% (conservative)	3.51	2.23	5.74
12% / 15%	4.7	4.23	8.93
14% / 17% (base case)	5.9	5.08	10.98
16% / 20%	7.1	6.79	13.89
18% / 22% (optimistic)	8.3	7.93	16.23

Net benefit remains positive for both interventions at every tested RRR. The break-even RRR, the point at which gross healthcare cost savings exactly offset total supplementation costs at 100% adoption, is approximately 4.2% for Ca+VitD and 8.1% for VitK2 at 2025 supplementation costs. The base-case RRRs of 14% and 17%, respectively, therefore remain well above the system-level break-even thresholds.

Both thresholds are below the lower bound of the tested sensitivity range, confirming that the positive net benefit finding is robust to a material downward revision of the efficacy assumption. Even under the most conservative tested scenario, with RRRs of 10% for Ca+VitD and 12% for VitK2, combined net benefit remains approximately €5.74 billion annually.

Parameter 2: Population Coverage

The base case models 100% supplementation of the eligible population as a policy-facing upper bound.

The sensitivity range tests coverage from 25% to 100%. The 71% coverage scenario is included as an analytically significant intermediate, reflecting the average country-level treatment gap reported by SCOPE 2021. It should not be interpreted as the population-weighted proportion of untreated individuals across the EU27+UK, which is approximately 62% based on the application of country-specific treatment-gap estimates. Net benefit scales linearly with coverage.

Even at 25% coverage, the combined net benefit is approximately €2.75 billion annually. Under the 71% coverage sensitivity scenario, supplementation would generate approximately €7.80 billion in combined net benefit, preventing approximately 986,000 fractures annually, at total supplementation expenditure of approximately €5.03 billion.

Coverage	Ca+VitD Avoided Fx	Ca+VitD Net €bn	VitK2 Avoided Fx	VitK2 Net €bn	Combined Net €bn
50%	322,333	2.95	371,835	2.54	5.49
71% (average treatment-gap scenario)	457,713	4.19	528,005	3.61	7.8
75%	483,500	4.43	557,752	3.81	8.24
100% (base case)	644,666	5.9	743,669	5.08	10.98

Parameter 3: Supplement Cost Sensitivity

The supplement cost input is tested at $\pm 20\%$ and $\pm 40\%$ from the base-case 2025 pricing, spanning a broad range of potential future cost conditions.

Cost Multiplier	Ca+VitD Net €bn	Ca+VitD BCR	VitK2 Net €bn	VitK2 BCR
×0.60 (−40%)	6.9	5.62	6.92	3.51
×0.80 (−20%)	6.4	4.22	6	2.63
×1.00 (base case)	5.9	3.37	5.08	2.11
×1.20 (+20%)	5.4	2.81	4.16	1.75
×1.40 (+40%)	4.91	2.41	3.24	1.5

Ca+VitD net benefit remains comfortably positive across the entire tested range, with a BCR above 2.4 even at 40% cost inflation. VitK2 net benefit is more sensitive to cost assumptions, ranging from approximately €6.92 billion at −40% cost to €3.24 billion at +40% cost, reflecting its larger absolute supplementation cost base. Nonetheless, VitK2 net benefit remains positive at every tested cost level, with a BCR of approximately 1.50 even under the most adverse cost assumption. A 40% reduction in VitK2 supplementation cost increases its net benefit to approximately €6.92 billion, compared with €5.90 billion for Ca+VitD at its base-case cost, illustrating the material impact that lower MK-7 pricing could have on the relative economics of the two interventions.

Parameter 4: Cost Perspective Sensitivity

The base case adopts the direct hospital healthcare cost perspective, capturing only acute fracture episode costs.

Cost Perspective	Ca+VitD Gross €bn	Ca+VitD Net €bn	Ca+VitD BCR	VitK2 Gross €bn	VitK2 Net €bn	VitK2 BCR
Direct hospital (base case)	8.39	5.9	3.37	9.68	5.08	2.11
Expanded direct healthcare costs (acute + disability)	12.78	10.29	5.14	14.74	10.14	3.21

The sensitivity analysis tests two alternative perspectives: “an expanded direct healthcare cost perspective incorporating SCOPE 2021’s disability cost estimate (adding €19.0 billion in long-term disability costs to the €36.3 billion in acute costs documented for 2019, a multiplier of 1.52 applied to gross HCCS), and an out-of-pocket perspective applying country-specific OOP expenditure shares to the HHC per fracture event (as documented in Table 5.2.3).

Under the expanded direct healthcare cost perspective, Ca+VitD net benefit increases to approximately €10.29 billion and VitK2 net benefit to €10.14 billion, with BCRs of 5.14 and 3.21, respectively. The inclusion of long-term disability costs materially strengthens the economic case for both interventions by increasing the monetised benefit associated with each avoided fracture.

Under the direct hospital cost perspective, nine countries show a negative VitK2 net benefit. The expanded direct healthcare cost perspective substantially improves the economic return in these markets by recognising disability costs that are excluded from the base-case analysis. This demonstrates that the negative net benefit observed in some countries under the base case is sensitive to the scope of fracture-related costs included in the model and should not be interpreted as evidence of an absence of broader economic value.

Parameter 5: Eligible Population Definition

The base case uses 34.6 million adults aged 50 and over for Ca+VitD and 32.9 million aged 55 and over (95% of the 50+ population) for VitK2. The sensitivity analysis tests $\pm 5\%$ and $\pm 15\%$ adjustments to the eligible population, spanning the range from a more restrictive definition (e.g., restricting to confirmed diagnosed osteoporosis with T-score ≤ -2.5 and at least one additional fracture risk factor, reducing the eligible population by approximately 10–15%) to a more inclusive definition (e.g., extending to high-risk osteopenic individuals, which could increase the eligible population by up to 5%).

Population Multiplier	Ca+VitD Net €bn	VitK2 Net €bn	Combined Net €bn
×0.85 (more restrictive)	5.02	4.32	9.34
×0.90	5.31	4.57	9.88
×0.95	5.61	4.83	10.44
×1.00 (base case)	5.9	5.08	10.98
×1.05 (more inclusive)	6.2	5.33	11.53

Net benefit is moderately sensitive to the eligible population definition but remains substantially positive across the entire tested range. Even when the eligible population is reduced by 15%, combined net benefit remains approximately €9.34 billion annually. The stability of the result across this range reflects the positive benefit-cost ratios of both interventions at the EU27+UK aggregate level (3.37 for Ca+VitD and 2.11 for VitK2). Because both healthcare cost savings and supplementation expenditure scale with the eligible population, changes in population size affect absolute net benefit proportionally while leaving the aggregate benefit-cost ratio unchanged.

Additional Analysis: Long-Term Cost Inflation and Return-on-Investment Sensitivity

The base case projects supplementation costs forward using country-specific inflation assumptions while holding healthcare cost savings per fracture event constant in nominal terms. This creates a progressively less favourable economic ratio over time, particularly for higher-cost interventions such as VitK2. This sensitivity examines the impact of differential growth in supplementation expenditure relative to gross healthcare cost savings on the net return per €1 spent over the 2025–2035 projection period.

5.7. Summary and Policy Implications

5.7.1. Summary of findings

The cost-savings model demonstrates that supplementation of the EU27+UK estimated osteoporosis population with calcium and vitamin D and with vitamin K2 (MK-7) can generate substantial net economic benefits under a conservative hospital-cost-only framework, with larger estimated benefits when broader societal costs are considered.

Under the 100% adoption base case in 2025, Ca+VitD supplementation of 34.6 million adults aged 50 and over prevents approximately 644,666 fragility fractures annually and generates a net population benefit of €5.90 billion, with a benefit-cost ratio of 3.37. VitK2 supplementation of 32.9 million adults aged 55 and over prevents approximately 743,669 fractures annually and generates a net population benefit of approximately €5.08 billion, with a benefit-cost ratio of 2.11. Combined, the two interventions prevent approximately 1.39 million fractures annually and generate a net benefit of approximately €10.98 billion against total supplementation expenditure of approximately €7.08 billion.

These findings remain positive across the sensitivity scenarios tested. Net benefit remains positive for Ca+VitD at an RRR above approximately 4.2%, compared with the 14% base-case assumption, and for VitK2 at an RRR above approximately 8.1%, compared with the 17% base-case assumption. Net benefit also remains positive at the EU27+UK aggregate level across all tested supplementation-cost and eligible-population assumptions. Under the expanded direct healthcare cost perspective, incorporating long-term disability costs alongside acute fracture costs, combined net benefit increases to approximately €20.43 billion annually, comprising €10.29 billion for Ca+VitD and €10.14 billion for VitK2. However, the broader cost perspective does not eliminate all country-level negative VitK2 results.

The 2025–2035 projection shows that the potential gross healthcare cost savings associated with supplementation increase as the modelled osteoporosis population and number of avoided fractures grow. Combined avoided fractures increase from approximately 1.39 million in 2025 to 1.60 million in 2035, while combined gross HCCS rises from approximately €18.06 billion to €20.79 billion. However, supplementation costs increase faster than gross savings under the model assumptions, causing the benefit-cost ratios to decline over time. Ca+VitD BCR decreases from 3.37 to 2.63, while VitK2 BCR decreases from 2.11 to 1.64. Consequently, combined annual net benefit declines from approximately €10.98 billion in 2025 to €10.34 billion in 2035, while remaining substantially positive throughout the projection period.

5.7.2. Policy implications

The findings have specific implications for EU member states, EU institutions, and the food supplement industry. Supplementation has the potential to offset healthcare expenditure associated with osteoporotic fractures. At a combined benefit-cost ratio of approximately 2.55, gross healthcare cost savings of €18.1 billion compare with total supplementation expenditure of approximately €7.08 billion under the 2025 base case. At 100% adoption, the model therefore estimates a combined annual net benefit of approximately €10.98 billion for Ca+VitD and VitK2. These estimates are based on direct hospital costs and exclude broader economic consequences such as long-term disability, productivity losses, informal care and quality-of-life impacts. The expanded direct healthcare cost sensitivity analysis demonstrates that inclusion of disability costs materially increases the estimated economic benefit.

The broader relevance of food supplementation within European public health policy is supported by Christie et al. (2025), a peer-reviewed review published in *Frontiers in Nutrition*. The authors identify micronutrient inadequacy and the role of food supplements as under-recognised in public health and clinical practice and call for a more integrated approach to nutrition policy. They also cite Weaver, Bischoff-Ferrari and Shanahan (2019), which estimated that Ca+VitD supplementation among adults with osteoporosis in the EU could prevent more than half a million fractures annually and generate approximately €5.7 billion in annual net cost benefit. The present analysis updates the Ca+VitD economic assessment using more recent population, fracture and cost inputs and extends the modelling framework to VitK2 (MK-7).

The treatment gap represents a potentially important target population for supplementation strategies. Approximately 21.5 million individuals estimated to have osteoporosis across the EU27+UK were not receiving pharmacological treatment for fracture prevention in 2025, based on the application of country-level treatment gap estimates to the modelled osteoporosis population. Separately, the model's 71% coverage sensitivity scenario, reflecting the average country-level treatment gap reported by SCOPE 2021, produces an estimated annual net benefit of approximately €7.80 billion and approximately 986,000 avoidable fractures when the results of the two independently modelled interventions are considered together. These figures should not be interpreted as outcomes specifically calculated for the 21.5 million untreated population. The geographic distribution of the treatment gap should therefore be considered alongside country-level fracture incidence, healthcare costs and supplementation economics when identifying priority markets and policy opportunities.

The Ca+VitD results provide a strong economic basis for considering targeted public support or reimbursement. At a benefit-cost ratio of 3.37 and an average annual supplementation cost of €71.85 per user, the model estimates that each euro of Ca+VitD expenditure generates approximately €3.37 in gross hospital cost savings at the EU27+UK aggregate level. The sensitivity analysis further indicates a break-even relative risk reduction of approximately 4.2%, compared with the 14% base-case assumption. Country-level results should nevertheless inform reimbursement decisions because healthcare costs, fracture incidence and supplementation expenditure vary across markets.

VitK2 presents a more heterogeneous country-level economic profile. At current modelled prices, VitK2 produces positive net benefit in 19 of 28 countries under the direct-hospital-cost perspective, while nine countries, Bulgaria, Croatia, Czechia, Estonia, Latvia, Lithuania, Luxembourg, Poland and Romania, have BCRs below 1.0. At the EU27+UK aggregate level, however, VitK2 remains net positive, generating approximately €5.08 billion in annual net benefit and a BCR of 2.11. Including long-term disability costs materially improves the results, increasing aggregate VitK2 net benefit to approximately €10.14 billion and the BCR to 3.21. This highlights the importance of both local supplementation prices and the scope of fracture-related costs included in country-level economic assessments.

MK-7 supplementation cost is an important determinant of VitK2's economic performance. A 20% reduction in the modelled 2025 supplementation cost increases annual VitK2 net benefit from approximately €5.08 billion to €6.00 billion and increases its BCR from 2.11 to approximately 2.63. A 40% reduction increases net benefit to approximately €6.92 billion and the BCR to 3.51. The net-benefit crossover with Ca+VitD at its base-case cost occurs at approximately an 18% reduction in VitK2 supplementation cost. These findings indicate that lower MK-7 prices, whether resulting from scale, competition, procurement or other market developments, could materially strengthen its system-level economics. The model does not, however, establish that these price reductions will occur.

The sensitivity analyses indicate that the aggregate economic conclusions remain positive across the range of assumptions tested. At the most conservative efficacy scenario tested, 10% RRR for Ca+VitD and 12% for VitK2, combined annual net benefit remains approximately €5.74 billion. Reducing the

eligible population by 15% produces combined net benefit of approximately €9.34 billion. Under the expanded direct healthcare cost perspective, combined net benefit increases from approximately €10.98 billion to €20.43 billion. These results demonstrate that the aggregate positive net benefit is not dependent on a single efficacy, supplementation-cost, population-size or cost-perspective assumption, although the magnitude of the benefit and country-level results vary materially between scenarios.

The demographic trajectory reinforces the longer-term relevance of fracture prevention. Combined avoided fractures increase from approximately 1.39 million in 2025 to 1.60 million in 2035, while combined gross healthcare cost savings increase from approximately €18.06 billion to €20.79 billion. However, supplementation expenditure increases faster than gross savings under the model assumptions, resulting in declining BCRs over time. Combined net benefit consequently decreases from approximately €10.98 billion in 2025 to €10.34 billion in 2035, while remaining positive throughout the projection period.

6. APPENDIX

6.1. *The Epidemiologic Burden of Osteoporotic Fractures in the EU27+UK*

Osteoporotic fractures represent one of the most burdensome and preventable consequences of bone ageing in Europe.³⁶ Osteoporosis and the 4.3 million fragility fractures per year that it causes cost the healthcare systems of Europe in excess of €56 billion each year, based on data for 2019.³⁷ This figure covers direct costs of incident fractures (€36.3 billion), long-term disability costs from prior fractures (€19.0 billion), and pharmacological treatment (€1.6 billion). When the value of quality-adjusted life years lost is incorporated, the cost of QALYs lost amounted to an additional €112.9 billion in 2019, underscoring that the direct cost figure substantially understates the true societal burden. At least 23.8 million EU residents are at high risk of osteoporotic fractures, and Europe faces an estimated 25% increase in osteoporotic fractures between 2019 and 2034, from 4.3 million to 5.3 million new fractures annually, driven entirely by the progressive ageing of European populations. Despite the scale of this burden, the average treatment gap across the EU27 and UK stands at 71%, with 14.0 million women eligible for pharmacological treatment remaining untreated in 2019, a number that has grown from 10.6 million in 2010.³⁸ The following sections document the epidemiological and economic dimensions of this burden at the EU27+UK level and by country, establishing the context within which calcium, vitamin D, and vitamin K2 supplementation offer their greatest preventive value.

6.1.1. *Scale and Prevalence of Osteoporosis*

Osteoporosis is a progressive skeletal disease characterised by low bone mineral density, micro-architectural deterioration of bone tissue, and consequent susceptibility to fracture from minimal or no trauma. Globally, the GBD 2019 Fracture Collaborators documented 178 million new fractures in 2019,³³ a 33.4% increase in absolute numbers since 1990, with the burden rising across all age groups but concentrated overwhelmingly in older adults. In Europe specifically, the International Osteoporosis Foundation's SCOPE 2021 report,³³ the most comprehensive and authoritative country-level scorecard for osteoporosis in Europe, estimated that 32.0 million individuals across the EU27, Switzerland, and the UK were living with osteoporosis in 2019, of whom 25.5 million were women and 6.5 million were men.

Updating the SCOPE 2021 baseline to 2025 using country-specific demographic growth rates, the total number of individuals with osteoporosis across the EU27 and UK is estimated at approximately 34.6 million. By 2035, this population is projected to reach approximately 39.8 million, representing a 15.0%

³⁶ Kanis JA, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, McCloskey EV, Willers C, Borgström F. SCOPE 2021: a new scorecard for osteoporosis in Europe. *Arch Osteoporos.* 2021;16(1):82.

³⁷ Kanis JA et al., SCOPE 2021: a new scorecard for osteoporosis in Europe. *Osteoporosis International* 2021;32(11):2105–2106.

³⁸ Willers C et al., Osteoporosis in Europe: a compendium of country-specific reports. *Archives of Osteoporosis* 2022;17(1):23.

increase over the decade. This growth is driven by population ageing, as osteoporosis prevalence rises steeply with age and Europe's older population continues to expand.

The sex asymmetry in osteoporosis burden is one of the most pronounced of any chronic disease. Women account for 96.8% of the eligible population across all 28 countries in the model. This reflects the fundamental biology of female bone ageing: the decline in oestrogen production at menopause accelerates bone loss at a rate 5–10 times faster than age-related loss alone, with women losing 20–30% of bone mineral density in the first decade post-menopause. The [NICE clinical guideline CG146](#) documents the resulting age-prevalence gradient with precision: approximately 2% of women have osteoporosis at age 50, rising to 12% by the early 60s, 24% in the 70s, and approaching 50% at age 80 and over. More than one in three women and one in five men will sustain at least one osteoporotic fracture in their lifetime.

6.1.2. Country-Level Osteoporosis Burden (2019 Baseline, 2025 Estimates, 2035 Projections)

Five countries, Germany (6.0 million in 2025, rising to 6.6 million by 2035), Italy (4.8 million to 5.5 million), France (4.4 million to 5.1 million), the UK (4.1 million to 4.8 million) and Spain (3.3 million to 3.9 million) account for approximately 66% of the EU27+UK osteoporosis population in 2025 and collectively add approximately 2.2 million individuals by 2035.

Ireland faces the steepest relative growth between 2025 and 2035, with its osteoporosis population projected to increase from 258,638 to 341,367, representing a 32.0% increase. Latvia, Bulgaria, Croatia, and Romania show comparatively modest projected growth, although their absolute burdens remain significant, particularly Romania, where an estimated 1.13 million individuals were living with osteoporosis in 2025.

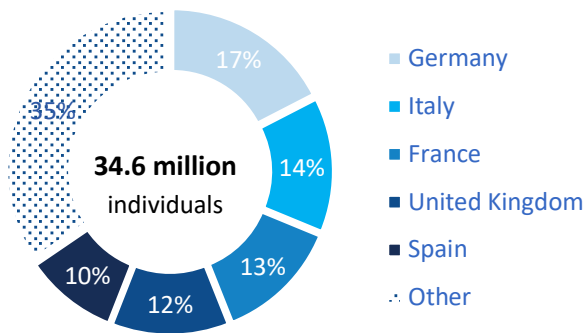


Figure 6.1.2.1: Burden Across EU27+UK, 5 countries hold ~66% of population with osteoporosis

The tables below present the complete country-level picture across all 28 countries, drawing on SCOPE 2021 for the 2019 baseline, the model's current estimates for 2025, and projections to 2035 derived by extending country-specific demographic CAGRs embedded in the model beyond the SCOPE 2021 2034 horizon.^{34, 39}

Country	Osteoporosis 2019	Osteoporosis 2025	Osteoporosis 2035	Growth 2019–2035
Austria	552,000	612,218	712,582	29.1%
Belgium	681,000	743,652	848,072	24.5%
Bulgaria	420,000	435,000	460,000	9.5%
Croatia	252,000	263,520	282,720	12.2%
Cyprus	50,000	59,697	75,859	51.7%
Czechia	572,000	652,457	786,552	37.5%
Denmark	328,000	370,716	441,910	34.7%
Estonia	82,000	88,643	99,715	21.6%
Finland	336,000	380,800	455,467	35.6%
France	3,991,000	4,406,592	5,099,245	27.8%
Germany	5,659,000	6,029,457	6,646,885	17.5%
Greece	684,000	744,800	846,133	23.7%
Hungary	559,000	616,200	711,533	27.3%
Ireland	209,000	258,638	341,367	63.3%
Italy	4,359,000	4,770,342	5,455,913	25.2%
Latvia	124,800	128,907	135,753	8.8%
Lithuania	181,000	193,906	215,416	19.0%
Luxembourg	29,600	34,928	43,808	48.0%
Malta	23,000	27,312	34,500	50.0%
Netherlands	976,000	1,122,596	1,366,923	40.1%
Poland	1,985,000	2,220,117	2,611,977	31.6%
Portugal	681,000	759,984	891,625	30.9%
Romania	1,071,000	1,133,388	1,237,369	15.5%
Slovakia	264,000	298,737	356,632	35.1%
Slovenia	125,000	140,060	165,161	32.1%
Spain	2,945,000	3,296,333	3,881,889	31.8%
Sweden	583,000	652,584	768,557	31.8%
UK	3,755,000	4,148,313	4,803,835	27.9%
EU27	27,722,400	30,441,584	34,973,563	26.2%
EU27 + UK	31,477,400	34,589,897	39,777,398	26.4%

Table 6.1.2.1: Individuals with Osteoporosis

³⁹ Hernlund E et al., Osteoporosis in the European Union: medical management, epidemiology and economic burden. Archives of Osteoporosis 2013;8(1–2):136.

Country	Osteoporotic fractures 2019	Osteoporotic fractures 2025	Osteoporotic fractures 2035	Growth 2019–2035
Austria	110,000	122,000	142,000	29.1%
Belgium	100,000	109,200	124,533	24.5%
Bulgaria	56,000	58,000	61,333	9.5%
Croatia	35,000	36,600	39,267	12.2%
Cyprus	6,600	7,880	10,013	51.7%
Czechia	91,000	103,800	125,134	37.5%
Denmark	86,000	97,200	115,867	34.7%
Estonia	7,900	8,540	9,607	21.6%
Finland	45,000	51,000	61,000	35.6%
France	484,000	534,400	618,400	27.8%
Germany	831,000	885,400	976,067	17.5%
Greece	99,000	107,800	122,467	23.7%
Hungary	86,000	94,800	109,467	27.3%
Ireland	32,000	39,600	52,267	63.3%
Italy	568,000	621,600	710,933	25.2%
Latvia	15,800	16,320	17,187	8.8%
Lithuania	23,000	24,640	27,373	19.0%
Luxembourg	4,000	4,720	5,920	48.0%
Malta	3,200	3,800	4,800	50.0%
Netherlands	99,600	114,560	139,493	40.1%
Poland	206,000	230,400	271,067	31.6%
Portugal	70,700	78,900	92,566	30.9%
Romania	103,000	109,000	119,000	15.5%
Slovakia	76,000	86,000	102,667	35.1%
Slovenia	16,600	18,600	21,933	32.1%
Spain	285,000	319,000	375,666	31.8%
Sweden	124,000	138,800	163,466	31.8%
UK	527,000	582,200	674,200	27.9%
EU27	3,664,400	4,022,560	4,619,493	26.1%
EU27 + UK	4,191,400	4,604,760	5,293,693	26.3%

Table 6.1.2.2: Individuals with osteoporotic fractures

Sources: SCOPE 2021 for the 2019 osteoporosis population baseline;³⁴ Hernlund et al. (2013), applied to Eurostat 2025 age-structured population data, for the 2025 model estimates;³⁶ and country-specific demographic growth projections for the 2035 estimates, derived by extending the 2025–2030 modelled CAGRs. Growth percentages for 2019–2035 are calculated from the 2019 baseline and projected 2035 population figures.

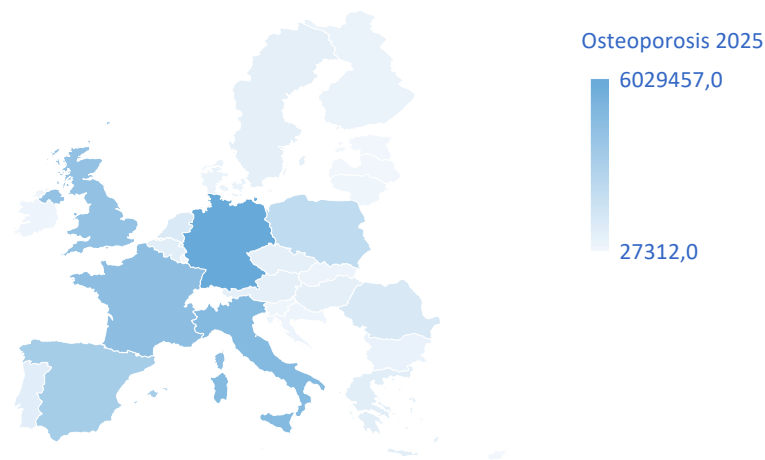


Figure 6.1.2.2: Estimated Number of Individuals Living with Osteoporosis by Country, EU27+UK, 2025

Poland (2.2 million individuals with osteoporosis in 2025) and Romania (1.1 million) represent the largest osteoporosis burdens among Central and Eastern European countries. Latvia, Bulgaria, Croatia, Romania, and Estonia are among the countries with the slowest projected growth in fracture incidence between 2019 and 2035, ranging from approximately 9% to 22%. In contrast, Ireland (+63.3%), Cyprus (+51.7%), Malta (+50.0%), and Luxembourg (+48.0%) show the steepest relative increases in osteoporosis prevalence counts over the same period. Ireland's osteoporosis population is projected to increase from 258,638 in 2025 to 341,367 by 2035, representing growth of 32.0% over ten years. Germany, Italy, France, and the UK are expected to experience the largest absolute increases in annual fracture numbers, collectively adding approximately 356,000 fractures by 2035 compared with 2025.

The female burden is overwhelming and structurally consistent across all 28 countries.

Of the estimated 34.6 million individuals with osteoporosis across the EU27+UK in 2025, approximately 33.5 million (96.8%) are women, compared with 1.1 million men (3.2%). The female share is remarkably consistent across the countries included in the model, ranging from approximately 96.6% in Cyprus to 97.0% in Latvia. This pronounced sex imbalance is consistent with the important role of post-menopausal oestrogen deficiency in accelerating bone loss, although the modelled distribution should not be interpreted as evidence that demographic, diagnostic, or healthcare-system differences have no influence on osteoporosis prevalence.

The estimated female osteoporosis population is particularly large in Germany (5.84 million), Italy (4.62 million), France (4.27 million), and the UK (4.02 million). Together, these four countries account for approximately 56% of all women estimated to have osteoporosis across the EU27+UK in 2025. The overall osteoporosis population is projected to increase from 34.6 million in 2025 to approximately 39.8 million by 2035. If the modelled 2025 sex distribution remains constant, the female osteoporosis population would reach approximately 38.5 million by 2035, representing an increase of approximately 5.0 million women over the decade.

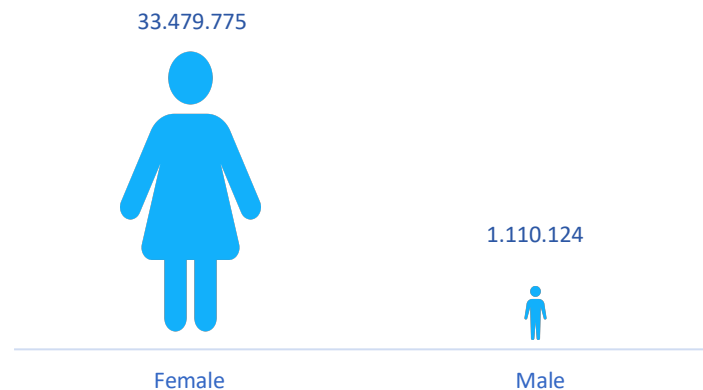


Figure 6.1.2.3: Average gender distribution of Osteoporosis in EU27+UK in 2025

Men with osteoporosis represent a smaller but clinically important population. In 2025, approximately 1.11 million men across the EU27+UK are estimated to have osteoporosis, accounting for 3.2% of the total modelled osteoporosis population. Assuming the same sex distribution in 2035, this population would increase to approximately 1.28 million men. Although osteoporosis is less prevalent among men in the model, male osteoporosis remains an important clinical concern, particularly given the serious consequences of fragility fractures and the potential for underdiagnosis and undertreatment.

The estimated male share of the osteoporosis population varies only modestly across countries, from approximately 3.0% in Latvia to 3.4% in Cyprus. In most countries, men account for approximately 3.2%–3.3% of the modelled osteoporosis population. These relatively small differences should be interpreted cautiously, as the country-level estimates do not independently establish the effects of mortality patterns, diagnostic practices, or healthcare-system characteristics on osteoporosis prevalence.

6.1.3. Fracture Incidence and the Fracture Event Rate

In 2025, an estimated 4.60 million new fragility fractures occurred across the EU27 and UK, equivalent to approximately 12,600 fractures every day, or one every seven seconds. SCOPE 2021 recorded 4.19 million fractures in 2019 and projected 5.23 million by 2034, a 24.7% increase over 15 years. The model's 2025 figure of 4.60 million is consistent with this trajectory, alongside a 9.9% increase in the estimated osteoporosis population between 2019 and 2025. By 2035, extending country-specific demographic growth rates embedded in the model, annual fragility fractures across the EU27 and UK are projected to reach approximately 5.29 million, representing a 26.3% increase from the 2019 baseline and a 15.0% increase from 2025.

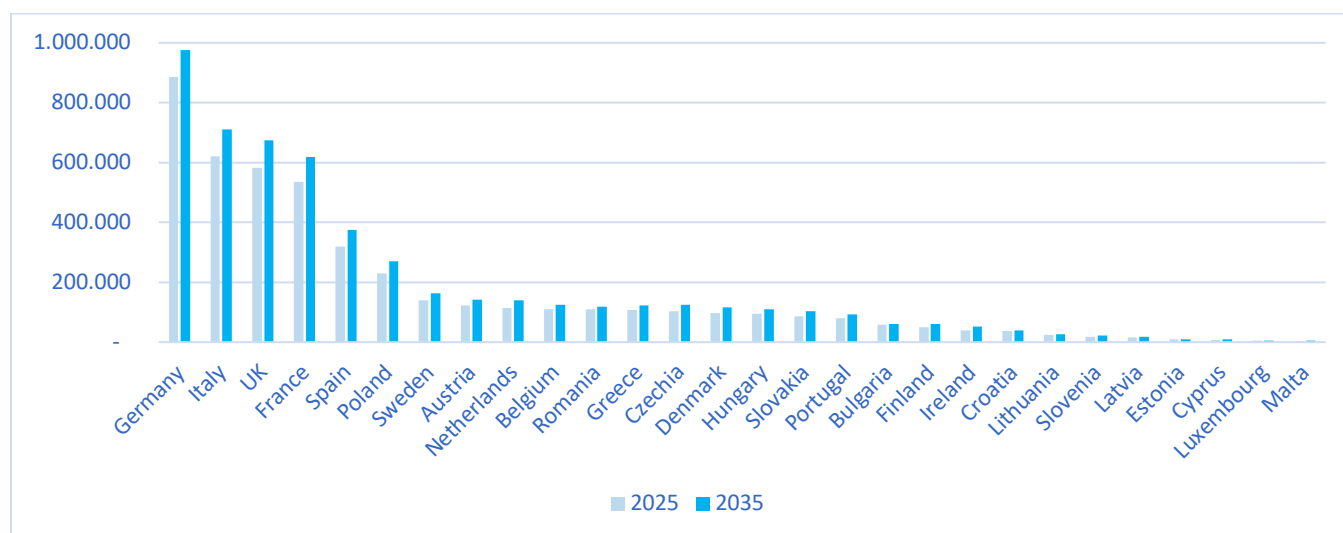


Figure 6.1.3.1: Estimated annual fragility fractures attributable to osteoporosis by country in 2025 and 2035

The fracture event rate, calculated as the annual number of fragility fractures divided by the estimated osteoporosis population, varies markedly across countries and represents one of the key epidemiological inputs in the cost-savings model. Across the EU27+UK in 2025, the aggregate fracture event rate is approximately 13.3%, ranging from 9.6% in Romania and Estonia to 28.8% in Slovakia. These variations reflect differences in the relationship between fracture incidence and the estimated osteoporosis population across countries, although they should not be interpreted solely as differences in individual fracture risk.

The hip fracture probability at age 50, the FRAX-derived country-level risk metric used by SCOPE 2021, illustrates the geographic gradient in fracture risk most clearly. Among women, this probability ranges from 7.0% in Romania to 25.1% in Sweden, a 3.6-fold differential. Northern and Western European countries consistently show the highest fracture probabilities, Sweden (25.1%), Denmark (22.3%), Finland (20.4%), and the UK (19.5%), while Central and Eastern European countries show the lowest, Romania (7.0%), Bulgaria (7.5%), Hungary (8.2%), and Slovakia (8.5%). This North–South and East–West gradient is well-established in the IOF literature and reflects, in part, differences in dietary calcium intake, sun exposure and vitamin D status, and body habitus and bone geometry. It has direct implications for the cost-savings model, as countries with higher baseline fracture incidence may generate greater absolute healthcare savings from effective fracture prevention. Sweden, Denmark, and Finland represent particularly favourable economic cases for expanded supplementation, with benefit-cost ratios for Ca+VitD of 7.05, 6.78, and 3.55, respectively, in 2025.

Vertebral fracture undercount. A critical methodological limitation acknowledged across the osteoporosis literature is the systematic underdiagnosis of vertebral fractures. Many vertebral fractures occur without significant trauma or clinical recognition and may therefore be absent from routine

healthcare statistics. The fracture incidence estimates underlying the model may not fully capture asymptomatic or clinically unrecognised vertebral fractures. Consequently, the estimated 4.60 million annual fractures in 2025 may understate the full clinical fracture burden. However, the extent to which this undercount affects the modelled healthcare cost savings depends on the costs and prevention effects associated with fractures not captured in the baseline incidence estimates.

Women sustain 96.8% of all osteoporotic fractures across the EU27 and UK, 4.46 million of the 4.60 million annual fractures estimated for 2025. This concentration reflects the combined effect of higher osteoporosis prevalence in women and their substantially longer post-menopausal life expectancy, which extends the period of elevated fracture risk across two to three decades. The burden is particularly acute in the 70–80 age band, where female osteoporosis prevalence approaches 24%, and in the over-80 population, where it approaches 50% (NICE CG146; Hernlund et al. 2013). Men account for approximately 147,825 fractures annually in 2025, 3.2% of the total. While modest in proportional terms, the clinical severity of male fractures is disproportionate. Men who sustain a hip fracture face an estimated one-year mortality of approximately 37%, compared to 20% in women, reflecting older age at fracture, higher comorbidity burden, and lower rates of post-fracture investigation and treatment (SCOPE 2021). Male osteoporosis is systematically underdiagnosed across the EU27+UK, and the fracture burden in men is therefore likely underestimated in routine statistics.

Both NICE and SCOPE 2021 identify men as a priority group for improved fracture liaison services and secondary prevention, making the male osteoporosis population a clinically important, if numerically smaller, component of the total burden addressed by the supplementation interventions modelled in this report.

6.2. Economic Burden of Osteoporotic Fractures

6.2.1. Total Direct Healthcare Costs in 2025

In 2025, the total direct hospital healthcare costs attributable to incident osteoporotic fractures across the EU27 and UK are estimated at €59.9 billion, derived by applying country-specific HHC per fracture event values to annual fracture incidence figures for each country. For historical context, SCOPE 2021 estimated direct costs associated with incident osteoporotic fractures at €36.3 billion in 2019. However, differences in reference year, costing assumptions and potentially the scope of costs included mean that these estimates should not be treated as directly comparable measures of healthcare cost growth.

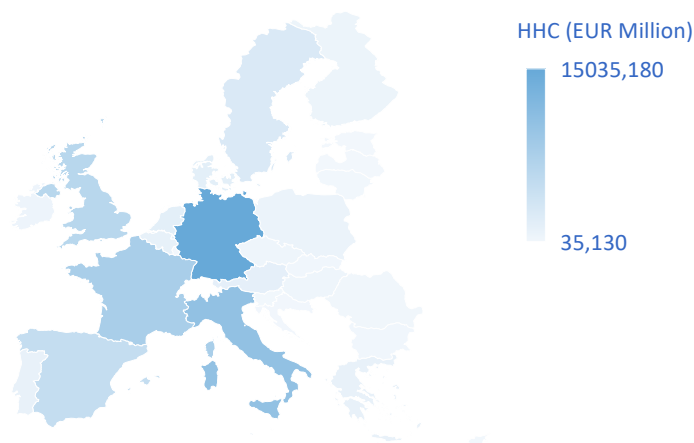


Figure 6.2.1.1: Direct Healthcare Costs by Country in 2025

SCOPE 2021 documented total direct costs, including ongoing long-term disability costs of €19.0 billion from prior fractures and €1.6 billion for osteoporosis assessment and pharmacological treatment, of €56.9 billion in 2019. The model captures only the incident fracture hospital cost component. This means the full societal cost savings from prevented fractures, including avoided long-term disability care, nursing home placement, and lost productivity, are not reflected in the net benefit figures presented in this report. The model's outputs are therefore conservative, and the true economic case for supplementation is materially stronger than the €5.9 billion Ca+VitD and €5.08 billion VitK2 net benefit figures suggest.

For context, SCOPE 2021 noted that the average direct cost of osteoporotic fractures per individual across the EU27+2 rose from €85 in 2010 to €109.10 in 2019, a 28% real-terms increase in a decade driven by rising healthcare unit costs and the growing proportion of older adults in the fracture population, whose more complex clinical profiles generate higher per-episode costs. By 2035, the model projects total direct hospital fracture costs across the EU27 and UK to reach €68.9 billion, a €9.0 billion increase from the 2025 baseline, driven by fracture volume growth. This trajectory underscores the compounding economic case for preventive action: every year in which supplementation adoption remains below its potential represents not only avoidable fractures and disability but a growing and recoverable burden on national healthcare systems across the region. Borgström et al. (2020) independently confirmed this dynamic, estimating that annual fragility fracture costs in the five largest EU countries plus Sweden were expected to increase by 27% by 2030, a projection entirely consistent with the present model's country-level growth rates over the same period.

6.2.2. Country-Level Economic Burden and Cost Concentration

The per-event cost varies 7.3-fold across the EU27+UK

From €2,618 in Slovakia and €2,641 in Romania to €19,074 in Sweden, the widest cost differential of any input variable in the model, and the primary structural determinant of country-level net benefit.

Sweden, Denmark (€17,092), Germany (€16,981), Italy (€16,801), and Spain (€15,506) sit at the high end, while Slovakia, Romania, Latvia (€3,141), Bulgaria (€3,403), and Poland (€3,495) sit at the low end. This sevenfold differential means that preventing one fracture in Sweden saves 7.3 times more than preventing one in Slovakia, producing dramatically different benefit-cost ratios, from 7.05 in Sweden to negative figures in Romania and Poland, despite identical intervention efficacy across countries. Countries with the highest HHC per event are also, not coincidentally, those with the highest healthcare system costs more broadly, where preventing a complex hip fracture with its surgical intervention, anaesthesia, acute ward stay, physiotherapy, and rehabilitation pathway generates the largest unit saving.

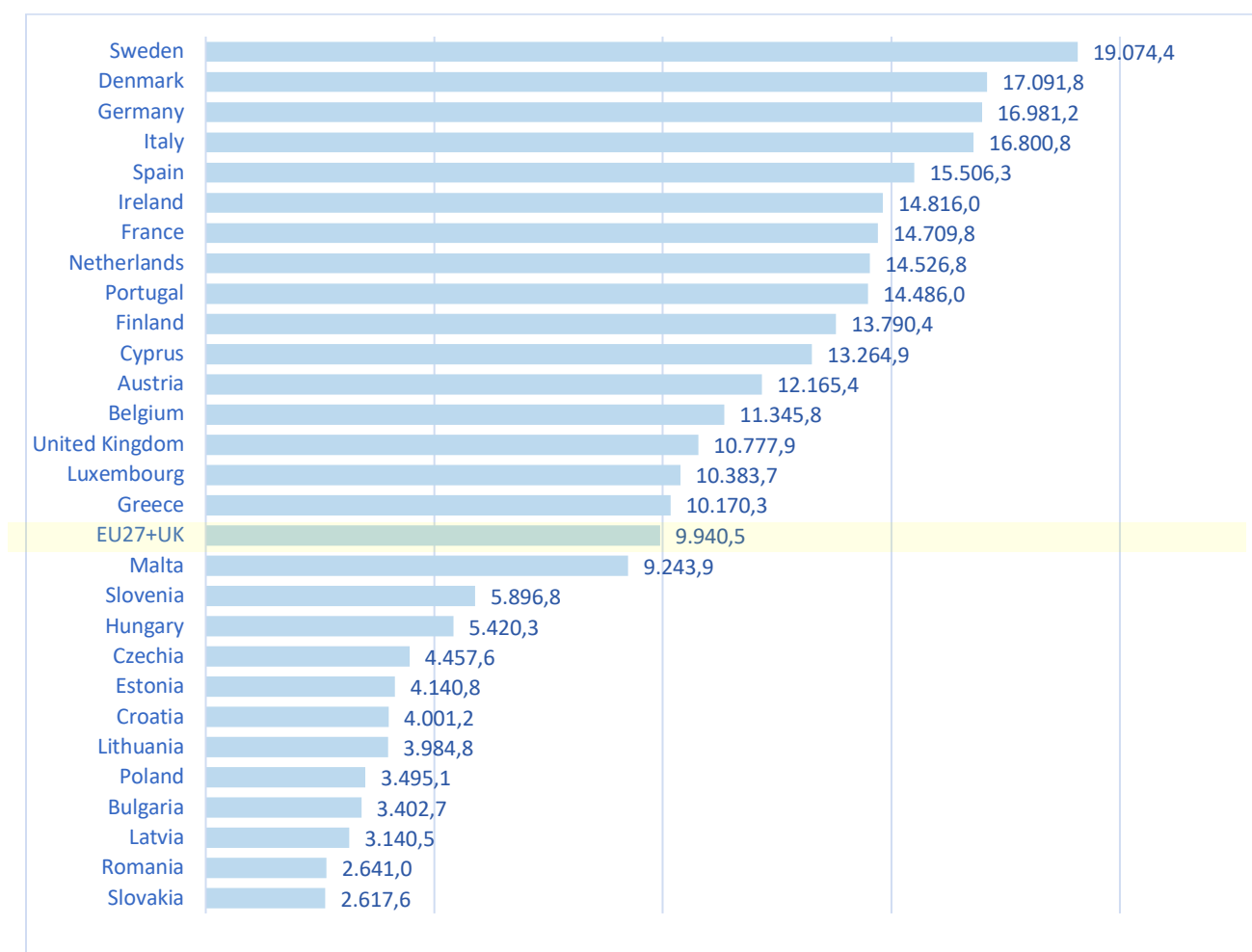


Figure 6.2.2.1: HHC per Fracture Event (EUR)

Note: The EU27+UK average represents the unweighted arithmetic mean of country-level healthcare costs per fracture event, with each country contributing equally. This figure is provided for cross-country comparison purposes. Aggregate healthcare cost savings in the economic model are calculated using country-specific fracture volumes and healthcare costs per event.

The fastest-growing cost burdens by 2035 are concentrated in smaller Western and Southern European countries.

Ireland faces the largest increase in total HHC from 2025 to 2035 with 32.5%. Cyprus 27.9%, Malta 27.4%, Luxembourg 26.0%, and the Netherlands 20.8% are all substantially above the EU27+UK average of 15.1%. The Netherlands is a particularly notable case: its HHC is projected to grow from €1.66 billion in 2025 to €2.01 billion by 2035, crossing the €2 billion threshold and overtaking Denmark as the seventh largest national fracture cost burden. Finland (20.7%) and Czechia (20.6%) also face above-average growth trajectories.

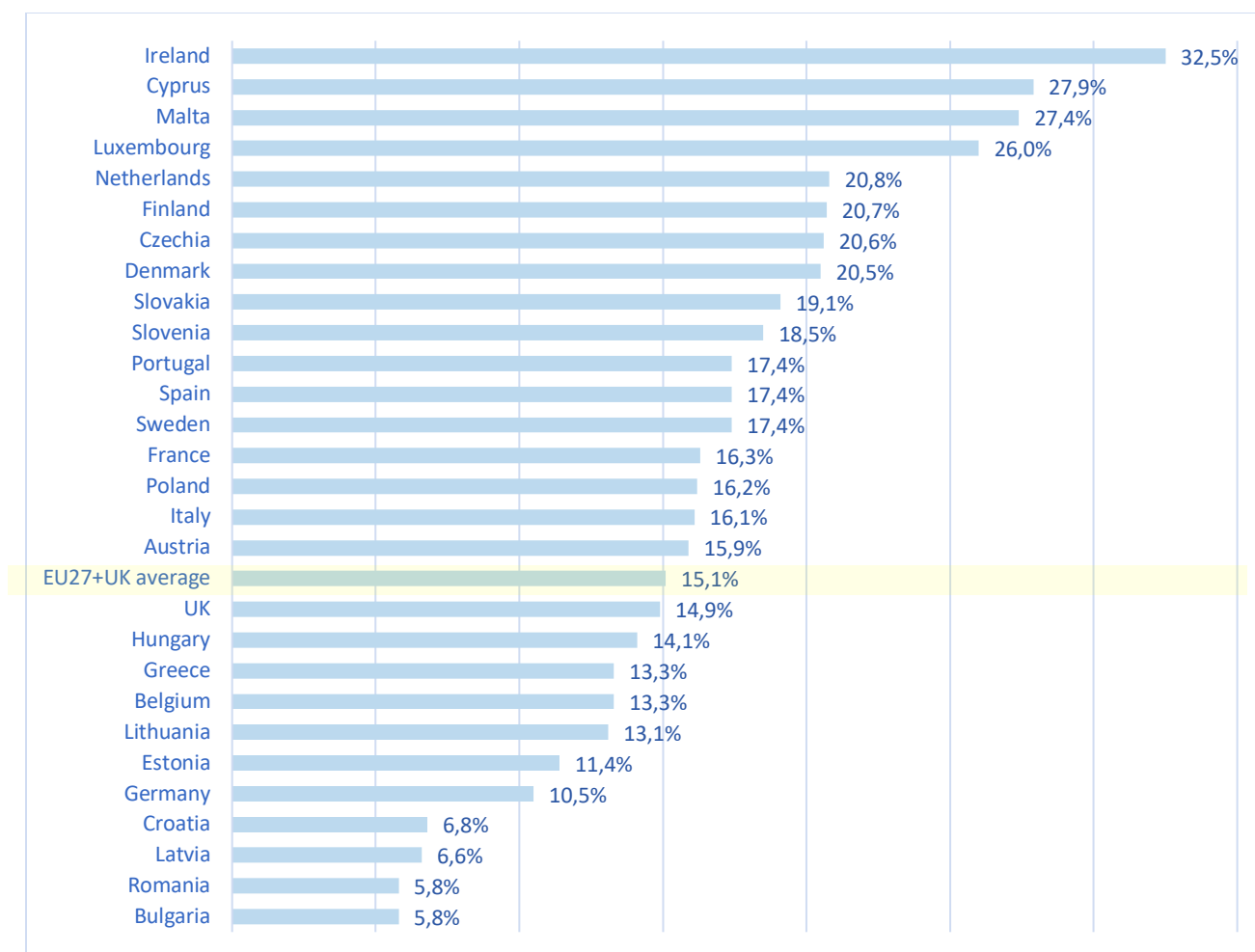


Figure 6.2.2.2: HHC growth from 2025 to 2035 for all 28 countries over the decade.

Note: The EU27+UK average represents the unweighted arithmetic mean of country-level percentage changes in total annual hospital healthcare costs attributable to osteoporotic fractures between 2025 and 2035, with each country contributing equally. It is presented for cross-country comparison purposes and does not represent the percentage change in aggregate EU27+UK hospital healthcare expenditure.

At the other end of the spectrum, Romania (+5.8%), Bulgaria (+5.8%), and Croatia (+6.8%) face the slowest cost growth, but this reflects low healthcare unit costs rather than a lower fracture burden, and these countries simultaneously carry some of the highest treatment gaps in Europe.

Total EU27+UK direct hospital fracture costs are projected to reach €68.9 billion by 2035

This trajectory is driven by growing fracture incidence, from 4.60 million in 2025 to 5.29 million by 2035, with hospital healthcare costs per fracture event held constant in nominal terms throughout the projection period. The resulting 15.1% increase in total direct hospital costs therefore reflects demographic changes and the associated growth in fracture volumes rather than healthcare cost inflation. Against this trajectory of rising costs, the total net benefit of Ca+VitD supplementation at 100% adoption remains broadly stable, at €5.9 billion in 2025 and approximately €6.0 billion by 2035, demonstrating a sustained economic case for preventive supplementation across the planning horizon.

6.2.3. Healthcare System Context and Patient-Level Economic Burden

The hospital healthcare costs captured in the model represent the public system perspective on fracture burden. Incorporating three additional health expenditure dimensions, total national health expenditure, PPP-adjusted per-capita spending, and out-of-pocket expenditure share, reveals a more complete and analytically richer picture of where osteoporotic fractures sit within each country's healthcare economy, and critically, why the patient-level economic case for supplementation is compelling universally across all 28 countries in ways the system-level model alone does not capture.

Fractures as a share of national health expenditure, proportional burden varies substantially.

Expressing annual fracture HHC as a percentage of total national health expenditure reveals that the proportional burden falls most heavily not on the largest economies but on Southern and Northern European countries with high fracture rates relative to their health system size. Greece carries the highest proportional burden at 5.32% of total health expenditure consumed by incident osteoporotic fractures in 2025, followed by Italy (5.07%), Cyprus (4.16%), Sweden (3.91%), Denmark (3.89%), and Portugal (3.82%). Germany, despite having the largest absolute fracture cost at €15.0 billion, absorbs this within a large health system, fractures represent 2.85% of Germany's total health expenditure. This proportional lens reframes the policy priority: for Greece and Italy, osteoporotic fractures are a

structural drain on health system resources at a scale that demands preventive action; for Germany the absolute scale is greater but the system-level pressure is comparatively lower.

Fracture cost as a multiple of per-capita health expenditure, affordability context.

Expressing HHC per fracture event as a multiple of the country's annual per-capita health expenditure (PPP-adjusted, 2023) provides the most meaningful cross-country comparability metric for fracture cost intensity.

Italy, Spain, Portugal, and Greece stand out: in each country, treating a single osteoporotic fracture costs between 2.9 and 3.5 times the country's entire annual per-capita health expenditure. Italy's HHC per fracture event of €16,801 represents 3.45 times the Italian per-capita health spend of €4,866. Portugal's €14,486 per event equals 3.10 times per-capita spend. This signals that fractures in Southern Europe, despite occurring in countries with moderate absolute healthcare costs, are catastrophically expensive relative to what the health system routinely spends per person annually. In contrast, Germany's high HHC per event of €16,981 represents only 2.04 times per-capita spend given its €8,306 per-capita health expenditure base. This distinction matters for policy: a fracture in Italy or Portugal is proportionally far more disruptive to the patient and the health system than the absolute euro figure suggests.

Out-of-pocket expenditure and the universal patient-level case for supplementation.

The single most analytically significant finding from integrating the health expenditure data is the following: in every one of the 28 countries modelled, the patient-facing cost of a fracture, measured as the HHC per fracture event multiplied by the country's out-of-pocket expenditure share, exceeds the annual supplement cost for both Ca+VitD and VitK2. Without exception, across all 28 countries.

Country	OOP Fracture Cost (€)	Ca+VitD Annual Cost (€)	VitK2 Annual Cost (€)
Austria	2,005	84	164
Belgium	2,440	83	162
Bulgaria	1,208	49	96
Croatia	375	56	110
Cyprus	2,380	72	141
Czechia	651	65	127
Denmark	2,389	93	180
Estonia	915	57	110
Finland	1,943	73	142
France	1,362	70	136
Germany	1,876	83	161
Greece	3,488	50	96

Country	OOP Fracture Cost (€)	Ca+VitD Annual Cost (€)	VitK2 Annual Cost (€)
Hungary	1,250	55	108
Ireland	1,674	163	317
Italy	3,973	70	136
Latvia	1,101	48	94
Lithuania	1,236	64	125
Luxembourg	911	174	339
Malta	2,859	80	156
Netherlands	1,748	99	193
Poland	554	58	112
Portugal	4,246	60	118
Romania	606	57	112
Slovakia	527	54	105
Slovenia	731	64	125
Spain	3,235	66	129
Sweden	2,472	81	157
UK	1,577	71	138
EU27	2,154	71.98	140.12
EU27+UK	2,081	71.85	139.87

Table 6.2.3: Out-of-pocket fracture cost per country vs annual cost of CalVitD / VitK2 in euros

Note: OOP fracture cost = HHC per fracture event 2025 × country OOP expenditure share (WHO Global Health Expenditure Database 2023). Supplement annual costs from DS Costs sheet, 2025. EU27 and EU27+UK values represent weighted averages rather than simple country averages. Out-of-pocket (OOP) costs per fracture are weighted by the annual number of fractures in each country, while annual supplementation costs are weighted by the respective eligible populations for Calcium + Vitamin D and Vitamin K2. Minor differences may arise from rounding.

The patient-level implication is unambiguous. Even in the countries where the system-level net benefit calculation shows negative figures, Romania, Poland, Bulgaria, Latvia, Lithuania, Estonia, Czechia, Croatia, and Luxembourg, the out-of-pocket cost of sustaining a single fracture vastly exceeds the annual cost of supplementation. A Romanian patient faces an estimated €606 out-of-pocket for a fracture, against a Ca+VitD supplement cost of €57 per year or a VitK2 cost of €112 per year. A Polish patient faces €554 out-of-pocket against €58 for Ca+VitD. In Bulgaria, Greece, and Latvia, countries where out-of-pocket expenditure shares exceed 34%, the patient-facing fracture cost is particularly acute relative to local income levels, making the economic case for supplementation from the patient's perspective even more compelling than these absolute figures suggest.

This finding provides additional context for interpreting negative net benefit results in certain countries under the hospital-cost-only framework. These results do not capture the wider economic burden of

osteoporotic fractures, including out-of-pocket expenditures borne by patients. Considering these additional costs may strengthen the broader economic case for preventive supplementation. However, a positive patient-level economic return cannot be established solely by comparing the out-of-pocket cost of a fracture with the annual cost of supplementation, as the expected return also depends on baseline fracture incidence and the assumed relative risk reduction.

The high private health expenditure shares in Greece (45.9%), Latvia (36.4%), Portugal (35.5%), Bulgaria (38.1%), Lithuania (30.8%), Malta (33.3%), and the Netherlands (31.2%) further reinforce this point. In these countries, most fracture-related healthcare costs that fall outside the acute hospital episode, rehabilitation, physiotherapy, assistive devices, home nursing, are borne privately. The system-level HHC captures only the acute hospital component; the true private financial burden of a fracture, when post-acute costs are included, is substantially higher than the OOP figures above already indicate.

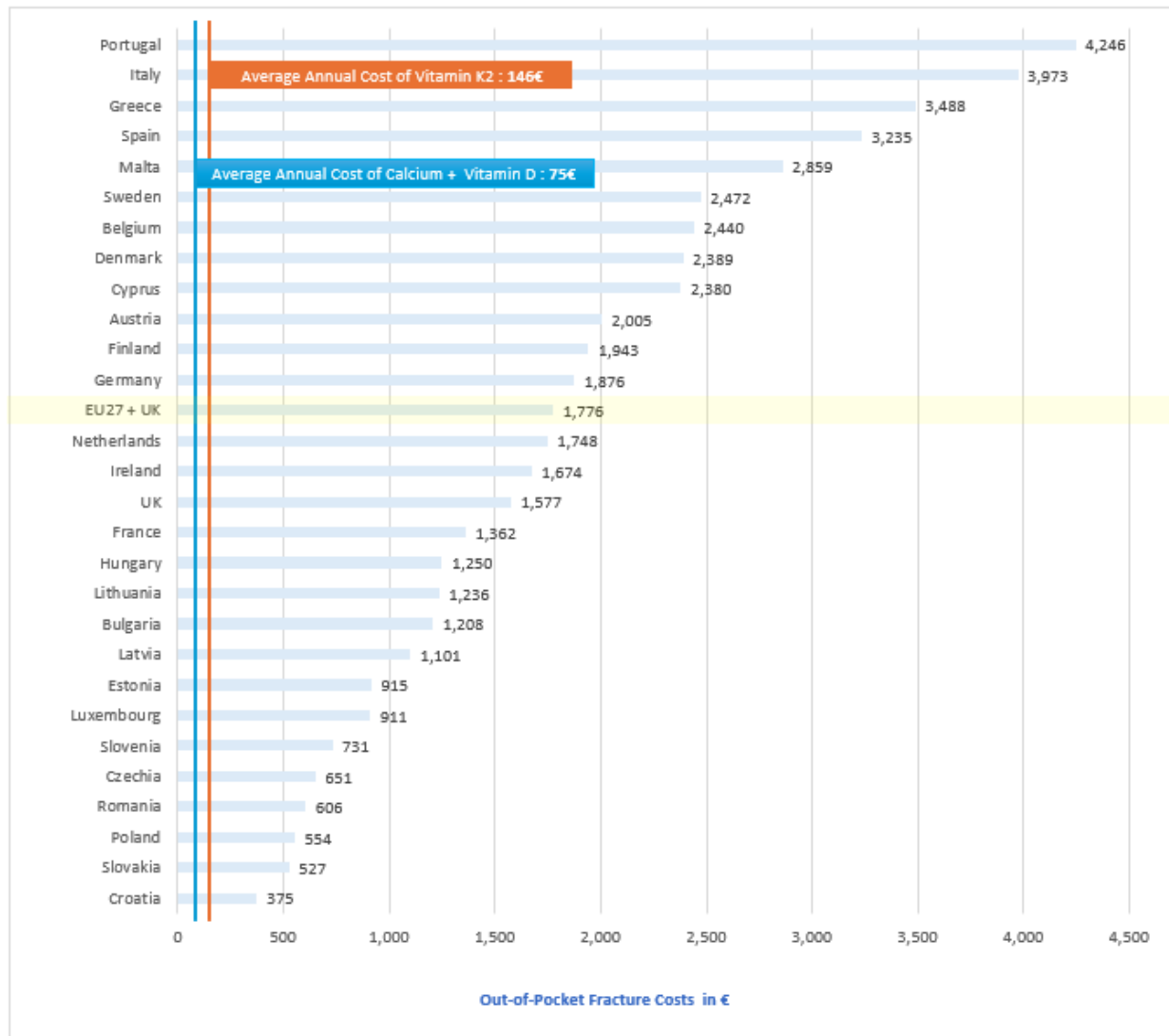


Figure 6.2.3.1: OOP Fracture Costs vs Annual Preventive Supplementation Costs Across EU27+UK

6.2.4. The Full Societal Burden: Beyond Hospital Costs

The direct hospital costs captured in the model represent the most measurable, but far from the complete, economic impact of osteoporotic fractures. SCOPE 2021 identifies three cost categories: incident fracture direct costs (€36.3 billion in 2019), long-term disability costs from prior fractures (€19.0 billion in 2019), and assessment and pharmacological treatment costs (€1.6 billion). The disability cost component reflects the burden of hip fracture survivors in long-term care, an enormous and growing cost that is completely absent from the model's HHC figures.

Beyond these direct costs, SCOPE 2021 documented more than a quarter of a million fracture-related deaths in the EU27+UK in 2019, a mortality burden comparable to or exceeding lung cancer, diabetes, and chronic lower respiratory disease across the region. Hip fractures carry a 20–30% one-year mortality rate in adults aged 65 and over, representing not only human suffering but substantial lost economic productivity, informal care burden on family members, and tax revenue forgone. The GBD 2019 Fracture Collaborators quantified 25.8 million years lived with disability (YLDs) globally from fractures in 2019, a 65.3% increase from 1990. The EU's share of this disability burden is disproportionately large given the advanced age of its population.

6.3. Target Population

6.3.1. Eligible Population Definition

The target population for the supplementation interventions analysed in this report is defined as adults aged 50 and over estimated to have osteoporosis residing in the EU27 and the UK. Osteoporosis is clinically defined by a bone mineral density T-score ≤ -2.5 ; however, the model uses country-level estimates of osteoporosis prevalence rather than restricting the eligible population to individuals with a confirmed clinical diagnosis. This population definition is consistent with the epidemiological approach applied in Weaver et al. (2019). For vitamin K2 (MK-7), the target population is more specifically adults aged 55 and over with osteoporosis or osteoporosis combined with additional fracture risk factors, reflecting the clinical trial populations in whom MK-7 benefit has been demonstrated (Knapen et al. 2013: mean age 59 years; Huang ZB et al. 2015: postmenopausal women with established osteoporosis).

In practice, given the near-zero prevalence of osteoporosis below age 50, the modelled eligible population is overwhelmingly concentrated in the 55+ age group for both interventions. The model does not separately restrict the Ca+VitD eligible population to 55+, applying it to the full estimated osteoporosis population aged 50+, consistent with the EFSA claim and Weaver 2019 methodology. The country-level osteoporosis population figures in the model, totalling 34.6 million in 2025 and projected to reach 39.8 million by 2035, already reflect this 50+ concentration, as the SCOPE 2021 and Hernlund 2013 source data apply age-stratified prevalence rates that are negligible below age 50.

6.3.2. Target Population Definition by Intervention

The eligible population for Ca+VitD is the full estimated osteoporosis population aged 50 and over, consistent with the EU-authorised Article 14 health claim conditions and the Weaver et al. (2019) methodology. The eligible population for VitK2 is restricted to adults aged 55 and over, representing approximately 95% of the total 50+ osteoporosis population, reflecting the clinical trial populations in whom MK-7 benefit has been most consistently demonstrated, Knapen et al. (2013, mean age 59 years)²⁰ and Huang ZB et al. (2015, postmenopausal women with established osteoporosis)²¹, and

consistent with the near-negligible prevalence of diagnosed osteoporosis below age 55 documented in Hernlund et al. (2013) and NICE CG146.

The weighted average annual supplement costs of €71.85 for Ca+VitD and approximately €139.87 for VitK2 are computed as total supplementation expenditure at 100% adoption divided by the respective eligible populations and are consistent with the country-level per-user costs presented in Table 6.4.1.

The higher VitK2 per-user cost reflects the current premium retail positioning of fermentation-derived MK-7 relative to the commodity supplement status of calcium and vitamin D in EU markets. Total supplementation expenditure at 100% adoption, €2.485 billion for Ca+VitD and approximately €4.60 billion for VitK2, is the product of these weighted average costs and the respective eligible population denominators and is consistent with the figures used throughout the cost-savings modelling in Chapter 6.

The full country-level supplement cost breakdown and the methodology underpinning the per-user cost derivation are set out in sections 6.4.1 and 6.4.4.

Characteristic	Calcium + Vitamin D
Age threshold	50 years and over
Clinical criterion	Estimated osteoporosis population (clinical reference definition: T-score ≤ −2.5 at femoral neck or lumbar spine)
Sex	Both women and men; women constitute 96.8% of eligible population in 2025
Menopausal status	Post-menopausal women particularly targeted by EU-authorised Article 14 claim
EU27+UK eligible population (2025)	34,589,897 (estimated osteoporosis population aged 50 and over)
EU27+UK eligible population (2035)	39,777,398
Source for eligible population	SCOPE 2021 (Kanis et al. 2021); ³³ Willers et al. 2022; ³⁴ Hernlund et al. 2013; ³⁵ Eurostat 2025
Regulatory basis	EU-authorised Article 14 claim (EU Regulation 2014/403): post-menopausal women aged ≥50 years; fracture risk reduction claim
Supplement dose modelled	1,000 mg calcium combined with 600 IU (15 µg) vitamin D daily
Annual supplement cost range (2025)	€48.25–€174.21 per user per year (country-specific, PPP-adjusted)
EU27+UK weighted average annual cost per user (2025)	€ 71.85
Total EU27+UK supplementation cost at 100% adoption (2025)	€2.485 billion

Table 6.3.2.1: Target Population Definition Calcium + Vitamin D, EU27+UK, 2025

Characteristic	Vitamin K2 (MK-7)
Age threshold	55 years and over
Clinical criterion	Estimated osteoporosis population aged 55 and over, including individuals with additional clinical fracture risk factors. The Knapen et al. (2013) anchor trial enrolled healthy postmenopausal women without requiring a diagnosis of osteoporosis. For modelling purposes, eligibility is restricted to an estimated osteoporosis population rather than the broader population of postmenopausal women, reflecting the higher-risk populations in which fracture benefits have been more consistently observed in the meta-analytic literature.
Sex	Both women and men; primary evidence base in postmenopausal women
Menopausal status	Post-menopausal women particularly targeted based on RCT evidence (Knapen et al. 2013) ²⁰
EU27+UK eligible population (2025)	32,860,402 (95% of the estimated osteoporosis population aged 50 and over, used as a proxy for the population aged 55 and over)
EU27+UK eligible population (2035)	37,789,032
Source for eligible population	SCOPE 2021 (Kanis et al. 2021); Willers et al. 2022; Hernlund et al. 2013; Eurostat 2025. The model applies a 95% age-based eligibility factor to the estimated osteoporosis population aged 50 and over to approximate the population aged 55 and over.
Regulatory basis	EU-authorized Article 13(1) bone maintenance claim (EU Regulation 432/2012; EFSA NDA Panel 2009). No Article 14 fracture risk reduction claim authorised.
Supplement dose modelled	180 µg/day MK-7
Annual supplement cost range (2025)	€93.93–€339.12 per user per year (country-specific, PPP-adjusted)
EU27+UK weighted average annual cost per user (2025)	€ 139.87
Total EU27+UK supplementation cost at 100% adoption (2025)	€4.60 billion

Table 6.3.2.2: Target Population Definition Vitamin K2 (MK-7), EU27+UK, 2025

6.3.3. The Treatment Gap, Where Supplementation Has Its Greatest Incremental Value

SCOPE 2021 identified one of the most striking findings in European osteoporosis management: in 2019, 71% of women at high fracture risk across the EU27+UK did not receive pharmacological therapy for osteoporosis.

This treatment gap has worsened over time, from 55% untreated in 2010 (10.6 million women) to 71% in 2019 (14.8 million women), despite the wide availability of effective pharmacological treatments.

Applying these country-specific treatment gap percentages to the 2025 osteoporosis population, the estimated number of individuals with diagnosed osteoporosis not receiving pharmacological treatment across the EU27 and UK in 2025 is approximately **21.5 million**, most of the total eligible population of 34.6 million. Countries are sorted by descending treatment gap percentage.

Country	Treatment Gap	Osteoporosis Pop. 2025	Untreated (est.)	Ca+VitD Annual Cost (€)	VitK2 Annual Cost (€)
Austria	55%	612,218	336,719	84.39	164.27
Belgium	56%	743,652	416,445	83.01	161.6
Bulgaria	87%	435,000	378,450	49.35	96.07
Croatia	74%	263,520	195,004	56.35	109.69
Cyprus	65%	59,697	38,803	72.41	140.96
Czechia	71%	652,457	463,244	64.99	126.52
Denmark	47%	370,716	174,236	92.56	180.18
Estonia	78%	88,643	69,141	56.65	110.27
Finland	48%	380,800	182,784	72.78	141.67
France	58%	4,406,592	2,555,823	70	136.27
Germany	52%	6,029,457	3,135,317	82.86	161.3
Greece	68%	744,800	506,464	49.56	96.47
Hungary	76%	616,200	468,312	55.32	107.69
Ireland	32%	258,638	82,764	162.61	316.54
Italy	67%	4,770,342	3,196,129	70.03	136.33
Latvia	82%	128,907	105,703	48.25	93.93
Lithuania	80%	193,906	155,124	64.25	125.08
Luxembourg	49%	34,928	17,114	174.21	339.12
Malta	62%	27,312	16,933	80.04	155.8
Netherlands	44%	1,122,596	493,942	98.94	192.6
Poland	75%	2,220,117	1,665,087	57.64	112.2
Portugal	64%	759,984	486,389	60.41	117.6
Romania	85%	1,133,388	963,379	57.34	111.62
Slovakia	83%	298,737	247,951	54.09	105.3
Slovenia	73%	140,060	102,243	64.44	125.45
Spain	69%	3,296,333	2,274,469	66.1	128.67
Sweden	38%	652,584	247,981	80.52	156.76
UK	61%	4,148,313	2,530,470	70.92	138.05
EU27	62.3%	30,441,584	18,975,950	69.83	135.94
EU27+UK	62.2%	34,589,897	21,506,420	69.96	136.18

Table 6.3.3.1: Osteoporosis Population, Treatment Gap, Estimated Untreated Population, and Annual Supplementation Costs by Country (2025)

Source: Treatment gap percentages from SCOPE 2021 (Kanis et al. 2021); Willers et al. 2022. Osteoporosis population 2025 from FSE model. Supplement annual costs from DS Costs sheet, 2025 values.

Note: EU27 and EU27+UK osteoporosis populations and estimated untreated populations represent the sum of country-level estimates. Aggregate treatment gaps are calculated as the total estimated untreated population divided by the total osteoporosis population, rather than as simple averages of national treatment gaps. Annual supplementation costs represent untreated-population-weighted averages of country-level costs. Minor differences may arise from rounding.

The treatment gap has a double significance for nutritional supplementation. First, it directly defines the population for whom Ca+VitD and VitK2 supplementation offers the greatest incremental value, individuals at confirmed elevated fracture risk who are not receiving pharmacological protection. Second, it establishes that the healthcare system is systematically failing to protect the majority of its most vulnerable patients, creating both a public health imperative and an economic opportunity for accessible, affordable supplementation to fill part of the prevention gap.



Figure 6.3.3.1: Treatment gap severity in EU27+UK

Three countries with the largest untreated absolute populations, Italy (3.2 million untreated), Germany (3.1 million), and Spain (2.3 million), are also among the highest net-benefit generators in the model, confirming that the greatest supplementation opportunity and the greatest economic return coincide geographically.

6.3.4. Population Risk Factor Profile

The eligible population of 34.6 million osteoporosis-diagnosed adults in the EU27 and UK in 2025 shares a common set of clinical and demographic characteristics that define their fracture risk profile and underpin the biological rationale for supplementation.

Age distribution. Osteoporosis prevalence is heavily concentrated in the oldest age groups, approximately 7–8% of adults in their 50s, rising to 12% in their 60s, 24% in their 70s, and approaching

50% in adults aged 80 and over (Hernlund et al. 2013; NICE CG146). The practical implication is that the majority of the eligible population is aged 65 and over, consistent with the clinical trial populations underlying the 14% RRR for Ca+VitD (Weaver et al. 2016: most RCT participants aged 65+) and the MK-7 trial evidence (Knapen 2013: mean age 59 years at enrolment, followed for 3 years).

Vitamin D insufficiency. Approximately 58% of Europeans have serum 25-hydroxyvitamin D levels below 30 ng/mL (Lips et al. 2006), implying that of the 34.6 million osteoporotic adults in 2025, approximately 20.1 million are vitamin D insufficient. This is the physiological condition under which Ca+VitD supplementation shows the greatest clinical benefit (Bertolacini da Silva et al. 2026; Fleet 2022), directly establishing the biological relevance of supplementation at population scale. Vitamin D deficiency is also listed explicitly by the WHO Bone Health and Ageing Initiative (2024) as a modifiable risk factor for fragility fractures, one of only six such factors identified, alongside smoking, alcohol, sedentary behaviour, low body weight, and falls.

Vitamin K2 status. Habitual dietary MK-7 intake in European populations typically ranges from 20–40 µg/day from fermented food sources (EFSA NDA Panel, EFSA Journal 2008;822), well below the 180 µg/day associated with full osteocalcin gamma-carboxylation in the Knapen et al. (2013) trial and the 90–180 µg/day threshold estimated to be required for optimal extra-hepatic vitamin K-dependent protein carboxylation (Bertolacini da Silva et al. 2026). Furthermore, the circulating levels of MK-7 required to reduce undercarboxylated osteocalcin increase with age (Bertolacini da Silva et al. 2026), precisely when the eligible population is entering its highest-fracture-risk period. This creates a structural micronutrient gap in the target population that dietary sources alone are unlikely to close.

6.3.5. Supplementation Adoption Scenario, Baseline Assumption

The healthcare cost savings model operates on a 100% supplementation scenario as its primary output, consistent with the Shanahan and de Lorimier (2016) methodology adopted in Weaver et al. (2019) and the CRN/Shanahan (2022) report. This scenario represents the maximum potential benefit, the total avoidable fractures and associated cost savings that would be realised if all members of the eligible estimated osteoporosis population supplemented at the modelled dose throughout the calendar year. It is not a forecast of likely adoption but a policy-facing upper bound on the intervention's value, enabling healthcare decision-makers to assess the benefit-cost ratio per supplemented individual and the aggregate opportunity cost of the current supplementation gap.

At 100% adoption in 2025, total supplementation costs across the EU27+UK are €2.485 billion for Ca+VitD, representing 34,589,897 individuals at a weighted average of €71.85 per user per year, and €4.60 billion for VitK2, representing 32,860,402 individuals at a weighted average of €139.87 per user per year. These figures are consistent with those used throughout chapter 6 and derived from the country-specific per-user costs presented in Table 6.4.1. Combined total supplementation expenditure at full adoption is €7.08 billion annually, against gross healthcare cost savings of €18.062 billion, yielding a combined gross-to-cost ratio of 2.55:1 before netting and a combined net population benefit of €10.98 billion.

Against the 100% adoption ceiling, the model's sensitivity analysis in section 5.6 tests net benefit across coverage scenarios of 25%, 50%, 71%, and 75% of the eligible population. The 71% coverage scenario is included as a sensitivity scenario reflecting the average country-level treatment gap reported by SCOPE 2021. Because treatment gaps vary substantially between countries, this scenario should not be interpreted as the population-weighted proportion of the EU27+UK osteoporosis population that is untreated; applying the country-specific treatment-gap estimates results in approximately 21.5 million untreated individuals, equivalent to around 62% of the Ca+VitD eligible population. At 71% coverage, Ca+VitD supplementation would prevent approximately 457,713 fractures annually and generate a net benefit of €4.19 billion; VitK2 supplementation would prevent approximately 528,005 fractures annually and generate a net benefit of €3.61 billion. Considered across the two independently modelled interventions, the 71% coverage scenario would result in approximately 986,000 avoidable fractures per year and a combined net benefit of approximately €7.80 billion annually, at a total supplementation cost of approximately €5.03 billion. These combined figures represent the arithmetic sum of the separate Ca+VitD and VitK2 scenarios and should not be interpreted as the number of unique fractures prevented through concurrent use of both interventions or as evidence of an additive clinical effect.

The calculation of yet-to-be-realised savings, adjusting the total potential savings for the proportion of the eligible population already supplementing, requires country-level supplement adoption data from EHPM European supplement use surveys or national nutrition surveys. Where available, these data are incorporated in the model's secondary scenario layer. The 21.5 million individuals estimated to receive no pharmacological treatment for fracture prevention, identified in the treatment gap analysis in section 6.3.3, represent a potentially important population for complementary supplementation strategies. However, pharmacological treatment status should not be interpreted as equivalent to current supplement use. Net benefit scales linearly with coverage for both interventions, as both gross savings and supplement costs are directly proportional to the number of supplemented individuals, meaning that every percentage point increase in Ca+VitD coverage generates approximately €59 million in additional annual net benefit and every percentage point increase in VitK2 coverage generates approximately €50.8 million, figures that grow each year as the osteoporosis population expands and fracture costs inflate.

6.4. Methodologies

6.4.1. Methodology for Estimating the Osteoporosis Population (EU27+UK)

The osteoporosis population estimates used in this model are derived in three stages: a 2019 baseline, an update to 2023 and 2025, and a projection to 2035.

The 2019 baseline is taken directly from the International Osteoporosis Foundation's SCOPE 2021 report (Kanis JA et al., Osteoporosis International 2021;32:2105–2106), which provides country-level estimates of the number of individuals with osteoporosis across the EU27, Switzerland, and the UK. SCOPE 2021 draws on the Hernlund et al. (2013) prevalence methodology (Archives of Osteoporosis 2013;8:136), which applies age-specific osteoporosis prevalence rates, derived from BMD-based population studies,

to age-structured national population data. Osteoporosis is defined as a T-score ≤ -2.5 at the femoral neck or lumbar spine by DXA, consistent with the WHO diagnostic criterion.

The update from the 2019 SCOPE 2021 baseline to the 2023, 2024, and 2025 model years applies country-specific compound annual growth rates (CAGRs) derived from Eurostat age-structured population projections (EUROPOP2023). The CAGR for each country is calculated as the annualised growth rate of the 50+ female and male populations, weighted by sex-specific osteoporosis prevalence rates from Hernlund et al. (2013). The resulting osteoporosis population CAGRs applied in the model range from 0.52% per year (Latvia) to 2.91% per year (Ireland), reflecting the differing pace of demographic ageing across EU member states.

The sex distribution of the osteoporosis population is held constant at country-specific proportions derived from SCOPE 2021, ranging from 96.6% female (Cyprus) to 97.0% female (Latvia), consistent with the biological universality of the oestrogen withdrawal mechanism driving post-menopausal bone loss.

The model's 2025 EU27+UK total of 34,589,897 individuals with osteoporosis is verified against the SCOPE 2021 trajectory, which projects from 32.0 million in 2019 toward 38.9 million by 2034, and is consistent with that trajectory at an intermediate point. The 2035 projection of 39,777,398 extends the country-specific CAGRs beyond the SCOPE 2021 2034 horizon.

For Ca+VitD, the eligible population is the full estimated osteoporosis population aged 50 and over, equal to the total model population. For VitK2, the eligible population is defined as the 55+ subset, estimated at 95% of the total 50+ osteoporosis population, reflecting the model's age-based eligibility assumption.

6.4.2. Methodology for Estimating Fracture Incidence and the Fracture Event Rate

Annual fracture incidence by country for the 2019 baseline is taken from SCOPE 2021 country-level data, which documents new fragility fractures by country derived from national hospital discharge databases, fracture registry data, and published epidemiological studies. The SCOPE 2021 2019 incidence figures range from 3,200 fractures (Malta) to 831,000 fractures (Germany), totalling 4,191,400 across the EU27+UK in 2019.

The fracture event rate (ER) for each country is calculated as annual fracture incidence divided by the estimated osteoporosis population:

$$\text{ER} = \text{Annual fractures} / \text{Osteoporosis population}$$

This rate expresses the number of annual fragility fracture events relative to the estimated osteoporosis population. It is an event-to-population ratio rather than an individual annual fracture probability, as individuals may experience more than one fracture within a year. The ER is held constant across the

projection period 2023–2035, reflecting the assumption that the age-specific fracture risk per osteoporotic individual does not change materially over this period in the absence of major changes in treatment or lifestyle. The absolute fracture count grows across the projection period solely through growth in the osteoporosis population denominator.

The aggregate 2025 EU27+UK fracture event rate is approximately 13.31%, calculated by dividing the total annual fracture events (4,604,760) by the estimated osteoporosis population (34,589,897).

Country-specific event rates range from 9.62% (Romania) to 28.79% (Slovakia). The high Slovakia event rate reflects a combination of a relatively small osteoporosis population and a fracture incidence figure disproportionately large relative to that population, consistent with SCOPE 2021's documentation of Slovakia's elevated FRAX-based fracture probability.

Annual fracture projections to 2035 are derived by applying the constant ER to the growing osteoporosis population in each country. The model's 2025 total of approximately 4.6 million fractures and 2035 projection of approximately 5.3 million fractures are consistent with SCOPE 2021's projected increase from 4.19 million (2019) to 5.23 million (2034).

A critical methodological limitation is the systematic underdiagnosis of vertebral fractures. Most vertebral fractures are asymptomatic or sub-clinical at presentation and are absent from the hospital discharge databases underpinning SCOPE 2021 incidence data. The SCOPE 2021 data, and therefore the model's event rate baseline, captures predominantly hip fractures and clinically presenting non-vertebral fractures. The true fracture incidence is materially higher than the figures used in the model, and all cost savings estimates presented in this report are conservative by this omission.

6.4.3. Methodology for Estimating Hospital Healthcare Costs per Fracture Event

The hospital healthcare cost per fracture event (HHC per event) represents the direct acute hospital cost of an incident osteoporotic fracture, encompassing surgical intervention where applicable, anaesthesia, inpatient ward costs, acute physiotherapy, and immediate discharge costs, but excluding post-acute rehabilitation, long-term care, and out-of-hospital costs.

Country-specific HHC per event values are derived from published national fracture cost studies, DRG-based hospital cost databases, and where direct national data are unavailable, from estimates scaled using relative healthcare price indices and PPP conversion factors from the WHO Global Health Expenditure Database (2023) and Eurostat healthcare price statistics.

The 2025 HHC per event values used in the model are presented in Figure 6.2.2.1 They range from €2,617.61 in Slovakia and €2,640.98 in Romania to €19,074.39 in Sweden, a 7.3-fold differential representing the widest cross-country range of any model input variable. The EU27+UK fracture-incidence-weighted average HHC per event is approximately €13,010, calculated by dividing total direct hospital fracture costs of €59.9 billion by approximately 4.6 million annual fractures.

The total direct hospital HHC attributable to incident osteoporotic fractures across the EU27+UK in 2025 is approximately €59,908 million (€59.9 billion), derived by applying country-specific HHC per event values to 2025 fracture incidence figures for each of the 28 countries. This figure is confirmed from the model's Sheet5 summation. The 2019 comparison from SCOPE 2021 was €36.3 billion for incident fracture direct costs, with the 2025 figure reflecting both the 9.9% increase in absolute fracture volume since 2019 and the impact of healthcare cost inflation across EU member states over the intervening six years.

HHC per event values are held constant in nominal terms across the 2025–2035 projection period. The model does not apply a nominal inflation adjustment to HHC per event, meaning that the growing gross HCCS across the trajectory reflects exclusively population-driven fracture volume growth rather than healthcare price inflation. This is a conservative assumption: healthcare costs in Europe have consistently inflated above general CPI, and applying a realistic healthcare inflation rate of 2–3% annually would materially increase gross savings and net benefit across the projection period.

6.4.4. Methodology for Estimating Supplement Costs

Annual supplement costs per user are derived from country-specific retail pricing surveys of food supplement products providing the modelled daily doses: 1,000 mg calcium combined with 600 IU vitamin D3 for Ca+VitD, and 180 µg menaquinone-7 (MK-7) for VitK2. Pricing data are sourced from national online pharmacy databases, major retail supplement platforms, and price benchmarking across the three to five most widely available product formats in each market, standardised to the lowest cost-per-day format to avoid premium product bias. All prices are inclusive of VAT where applicable and converted to euros using Eurostat PPP conversion factors for the household consumption of food and non-alcoholic beverages category.

The 2025 base year per-user annual costs are stored in the DS Costs sheet of the model and range from €48.25 (Latvia) to €174.21 (Luxembourg) for Ca+VitD, and from €93.93 (Latvia) to €339.12 (Luxembourg) for VitK2. The VitK2 cost is consistently 1.95 times the Ca+VitD cost across all 28 countries in 2025, reflecting the current premium market positioning of fermentation-derived MK-7 relative to the commodity supplement status of calcium and vitamin D in EU markets.

The EU27+UK weighted average annual supplement cost per user is €71.85 for Ca+VitD and €139.87 for VitK2, computed as total supplementation expenditure at 100% adoption divided by the eligible population.

Supplement costs are inflated forward annually using country-specific supplement price inflation rates derived from observed consumer price inflation in the food supplement category in each market. These rates are applied to each country's base year cost to generate year-by-year cost inputs through 2035. The inflation rates applied in the model range from 1.07% per year (Lithuania) to 5.07% per year (Romania) for the 2025–2026 period, converging toward a long-run rate of approximately 2.50% per year for most countries by 2033–2035 as inflationary pressures moderate. The model applies these

country-specific rates individually rather than a uniform EU-wide rate, preserving the structural cost differentials across markets throughout the projection period.

Total supplementation expenditure at 100% adoption is €2.485 billion for Ca+VitD (34,589,897 individuals at a weighted average of €71.85) and €4.60 billion for VitK2 (32,860,402 individuals at a weighted average of €139.87) in 2025.

6.4.5. Methodology for Estimating the Eligible Population by Intervention

The eligible population for each intervention is defined by three criteria: a clinical criterion, an age threshold, and a geographic scope.

The clinical reference criterion for osteoporosis is a bone mineral density T-score ≤ -2.5 , consistent with the WHO diagnostic standard. However, the modelled eligible populations are derived from country-level estimates of osteoporosis prevalence rather than confirmed individual diagnoses. Eligibility is therefore defined epidemiologically for the purposes of the economic model, with the applicable age thresholds and population adjustments specified separately for Ca+VitD and VitK2.

The age threshold differs by intervention. For Ca+VitD, the age threshold is 50 years and over, consistent with the EU-authorized Article 14 health claim for calcium and vitamin D in reducing the risk of osteoporotic fractures in post-menopausal women (EU Regulation 2014/403), and with the modelling approach in Weaver et al. (2019), which applied the relative risk reduction from Weaver et al. (2016) to an estimated osteoporosis population aged 50 and over. The Ca+VitD eligible population in 2025 is 34,589,897 individuals across the EU27 and UK.

For VitK2, the age threshold is 55 years and over, reflecting the clinical trial populations in whom MK-7 benefit has been investigated: Knapen et al. (2013) enrolled postmenopausal women with a mean age of 59 years, and the Huang ZB et al. (2015) meta-analysis concentrated its significant findings in women with established osteoporosis rather than the general postmenopausal population. The age restriction also reflects the relatively low prevalence of osteoporosis in younger age groups, approximately 2% of women at age 50 rising to 12% in the early 60s (Hernlund et al. 2013; NICE CG146). For modelling purposes, the VitK2 eligible population is estimated at 95% of the total osteoporosis population aged 50 and over, equivalent to 32,860,402 individuals in 2025. This 95% factor represents the model's age-based eligibility assumption rather than a count of clinically diagnosed individuals.

The geographic scope is the EU27 and UK, comprising 28 countries. Switzerland, which is included in some SCOPE 2021 analyses, is excluded from the model scope.

Both eligible populations grow across the projection period at the country-specific CAGRs documented in section 6.4.1, reaching 39,777,398 (Ca+VitD) and 37,789,032 (VitK2) by 2035.

6.4.6. Methodology for Estimating the Treatment Gap

The treatment gap is defined as the proportion of women at high fracture risk who are not receiving pharmacological therapy for osteoporosis. Country-specific treatment gap percentages are taken directly from SCOPE 2021 (Kanis JA et al. 2021) and Willers et al. (2022, Archives of Osteoporosis 17:23), which document the percentage of eligible women across EU member states who remain untreated despite meeting the clinical threshold for pharmacological intervention.

The treatment gap percentages range from 32% in Ireland, the lowest in the EU27+UK, to 87% in Bulgaria, with an unweighted country average of 71% across the EU27+UK. These country-specific percentages are applied to the respective 2025 osteoporosis populations to estimate the number of individuals not receiving pharmacological fracture protection. When weighted by the estimated osteoporosis population in each country, the aggregate EU27+UK treatment gap is approximately 62.2%.

The number of untreated individuals in 2025 is calculated as:

$$\text{Untreated} = \text{Osteoporosis population} \times \text{Treatment gap (\%)}$$

Summing across all 28 countries yields approximately 21.5 million untreated individuals across the EU27+UK in 2025, representing 62.2% of the total eligible Ca+VitD population. These individuals represent an important target population for nutritional supplementation as a prevention strategy, as they are estimated to have osteoporosis but are not receiving pharmacological fracture protection.

The treatment gap percentages used in the model are based on 2019 data reported in SCOPE 2021. These country-specific percentages are applied to the estimated 2025 osteoporosis populations to calculate the number of untreated individuals. SCOPE 2021 reported an increase in the average treatment gap between 2010 and 2019, from 55% to 71%. However, the model does not project changes in treatment gap percentages beyond 2019. Consequently, the estimated 21.5 million untreated individuals in 2025 should be interpreted as a modelled estimate based on historical treatment gap assumptions, rather than a direct measurement of treatment status in 2025.

6.4.7. Methodology for Estimating Out-of-Pocket Fracture Costs

The out-of-pocket (OOP) fracture cost represents the patient-facing financial burden of sustaining an osteoporotic fracture, measured as the component of the direct hospital cost borne by the patient rather than the public health system. It is calculated as:

$$\text{OOP fracture cost} = \text{HHC per fracture event} \times \text{OOP expenditure share}$$

OOP expenditure shares by country are sourced from the WHO Global Health Expenditure Database (2023), which reports the percentage of total health expenditure borne by households through out-of-pocket payments, net of health insurance reimbursement. These national healthcare expenditure shares are used as proxies to estimate the potential patient-borne component of osteoporotic fracture costs. They are not fracture-specific OOP expenditure rates. The OOP shares used in the model reflect 2021–2022 data for most member states.

OOP shares across the EU27+UK range from approximately 10.5% in France, where the comprehensive Assurance Maladie system covers most hospital costs, to 45.9% in Greece, where private co-payments and system-level gaps in public coverage result in nearly half of healthcare expenditure falling on patients directly.

The OOP fracture cost is not used as a primary model input in the base case benefit calculation, which adopts the direct hospital system perspective throughout. It is presented in Table 6.2.3 as a complementary analytical lens to illustrate the potential patient-level financial burden associated with osteoporotic fractures. The estimated OOP cost of a single fracture exceeds the annual cost of supplementation for both Ca+VitD and VitK2 in all 28 countries. However, this comparison does not constitute a patient-level cost-benefit analysis, as the cost of supplementation is incurred annually, whereas fracture-related expenditure depends on the probability of sustaining a fracture and the extent to which supplementation reduces that risk.

6.4.8. Methodology for the 2025–2035 Projection

The 2025–2035 projection is generated by extending four time-varying model inputs forward from the 2025 base year: the eligible osteoporosis population, annual fracture incidence, supplement costs per user, and total supplementation expenditure. Two model inputs are held constant across the projection period: the fracture event rate and the RRR for each intervention.

The eligible osteoporosis population grows at the country-specific CAGRs documented in section 6.4.1, derived from Eurostat EUROPOP2023 age-structured population projections. These CAGRs range from 0.52% per year (Latvia) to 2.91% per year (Ireland) and are applied compound from the 2025 base year to generate annual population estimates through 2035.

Annual fracture incidence in each country is updated each year by applying the constant country-specific fracture event rate to the growing osteoporosis population. This approach holds the aggregate fracture event rate constant within each country while allowing absolute fracture volumes to grow with the estimated osteoporosis population. It does not explicitly model changes in age-specific fracture rates or shifts in the age distribution of the osteoporosis population.

Supplement costs are inflated forward using the country-specific annual inflation rates documented in section 6.4.4, applied compoundly from the 2025 base year. These rates, derived from observed consumer price inflation in the food supplement category, decline gradually from approximately 2.5–

3.5% per year in most countries in 2025–2026 toward a long-run rate of 2.50% per year applied uniformly from 2033 onward.

HHC per fracture event is held constant across the projection period in nominal terms, as documented in Section 6.4.3. Consequently, growth in gross HCCS reflects exclusively the projected increase in fracture volumes rather than healthcare cost inflation. This assumption excludes potential increases in hospital treatment costs per fracture and may therefore underestimate future savings if those costs rise. However, it should not be interpreted as necessarily conservative under all future healthcare cost scenarios.

The RRR for each intervention, 14% for Ca+VitD and 17% for VitK2, is held constant throughout the 2025–2035 projection period. These values represent the model's base-case efficacy assumptions. The model does not incorporate potential changes in supplementation effectiveness over time, including those associated with treatment adherence, duration of supplementation or changes in the characteristics of the eligible population. The RRR is therefore treated as a constant parameter for projection purposes rather than as a demonstrated long-term clinical outcome.

6.4.9. Methodology for the Sensitivity Analysis

The sensitivity analysis is designed to test the robustness of the base case net benefit conclusion, that Ca+VitD and VitK2 supplementation generate positive net economic benefit across the EU27+UK, against the principal sources of uncertainty in the model. Five parameters are tested independently, with all other parameters held at base case values.

Parameter 1, Relative Risk Reduction.

The RRR is the most analytically significant model input, as both the avoided fracture count and gross HCCS are directly proportional to it. The tested range spans 10%–18% for Ca+VitD and 12%–22% for VitK2, providing conservative and optimistic scenarios around the respective base-case RRR assumptions of 14% and 17%. The break-even RRR, below which gross savings do not cover supplementation costs, is 4.2% for Ca+VitD and approximately 8.1% for VitK2 at 2025 prices, both substantially below the lower bound of the sensitivity range. Results are presented in Table 5.6.2.

Parameter 2, Population Coverage.

The base case 100% adoption scenario is tested against 25%, 50%, 71%, and 75% coverage. These percentages represent hypothetical supplementation uptake scenarios applied to the eligible population. The 71% scenario corresponds numerically to the unweighted average country-level treatment gap reported by SCOPE 2021, but does not represent the population-weighted EU27+UK treatment gap of approximately 62.2%. Net benefit scales linearly with coverage, as both gross savings and supplementation costs are directly proportional to the number of supplemented individuals. Consequently, the BCR remains unchanged across coverage scenarios. Results are presented in Table 5.6.2.

Parameter 3, Supplement Cost.

The supplement cost per user is varied by $\pm 20\%$ and $\pm 40\%$ from the 2025 base case values, spanning the plausible range from aggressive volume-driven price reduction (-40%) to regulatory cost burden or market concentration premium ($+40\%$). At $+40\%$ cost, the most adverse tested scenario, Ca+VitD net benefit remains at €4.91 billion (BCR 2.41) and VitK2 net benefit at €3.24 billion (BCR 1.50), confirming the robustness of the positive net benefit finding across the full tested cost range. Results are presented in Table 5.6.2.

Parameter 4, Cost Perspective.

The base case uses the direct hospital cost perspective, capturing only acute fracture episode costs. An expanded direct healthcare cost perspective is tested by applying a multiplier of 1.523 to gross HCCS, derived from the ratio of SCOPE 2021's total direct cost estimate (acute incident fractures €36.3 billion plus long-term disability costs €19.0 billion) to the acute incident cost alone (€36.3 billion), using 2019 data. This multiplier is applied uniformly across all countries as a modelling approximation, although the ratio of long-term disability costs to acute fracture costs may vary between healthcare systems. This scenario does not constitute a full societal cost analysis, as it excludes indirect costs such as productivity losses and informal care. Under this expanded direct healthcare cost scenario, the economic return from VitK2 supplementation improves across all nine countries with negative net benefit in the hospital-cost-only base case. However, Poland, Romania and Estonia remain below the break-even threshold, while the other six countries move into positive net benefit. Results are presented in Table 5.6.2.

Parameter 5, Eligible Population Definition.

The eligible population is varied by $\pm 5\%$ and $\pm 15\%$ from the base case, spanning the range from a more restrictive definition (e.g., requiring at least one additional clinical fracture risk factor beyond T-score ≤ -2.5) to a more inclusive definition (e.g., incorporating high-risk osteopenic individuals with T-score between -1.5 and -2.5). Net benefit scales proportionally with population size, and remains substantially positive across the full tested range. At $\times 0.85$ (15% population reduction), combined net benefit remains above €9.3 billion annually. Results are presented in Table 5.6.2.

An additional long-term economic sensitivity analysis examines the impact of country-specific supplementation cost inflation over 2025–2035 while holding hospital healthcare costs per fracture

constant in nominal terms. This analysis is presented separately from the five core sensitivity parameters in Section 5.6.2.

6.4.10. Methodology for Estimating the Total Economic Burden of Osteoporotic Fractures

The total direct hospital healthcare cost of incident osteoporotic fractures across the EU27+UK in 2025, €59.9 billion, is computed as the sum of country-level products of annual fracture incidence and HHC per fracture event:

$$\text{Total HHC} = \sum (\text{Fractures}_{\text{country}} \times \text{HHC per event}_{\text{country}})$$

The 28 country-level contributions sum to approximately €59,908 million (€59.9 billion). Germany contributes the largest share, followed by Italy, France, the UK, and Spain. These five countries account for the large majority of total EU27+UK direct fracture costs, reflecting their combination of large osteoporosis populations and mid-to-high HHC per fracture event values.

SCOPE 2021 estimated direct costs associated with incident osteoporotic fractures at €36.3 billion in 2019, compared with €59.9 billion estimated by the present model for 2025. Over this period, estimated annual fracture incidence increased from 4.19 million to 4.60 million events, representing growth of approximately 9.9%. However, the difference between the two cost estimates cannot be attributed solely to changes in fracture incidence and healthcare inflation without establishing that the underlying cost definitions, data sources and valuation methodologies are directly comparable. The 2019 figure is therefore presented as a historical reference point rather than as a directly comparable baseline for measuring healthcare cost inflation.

By 2035, applying constant HHC per event values (as documented in Section 6.4.3) to the projected annual fracture volume, total direct hospital fracture costs are projected to reach €68.9 billion, an approximately €9.0 billion increase from the €59.9 billion 2025 baseline, driven entirely by fracture volume growth. If a realistic healthcare cost inflation rate of 2.5% per year were applied to HHC per event values through the projection period, total direct fracture costs in 2035 would be approximately €88.2 billion, representing a substantially more adverse trajectory against which the €20.8 billion in combined gross savings generated by Ca+VitD and VitK2 supplementation by 2035 represents an even more compelling economic return.

F R O S T  S U L L I V A N