

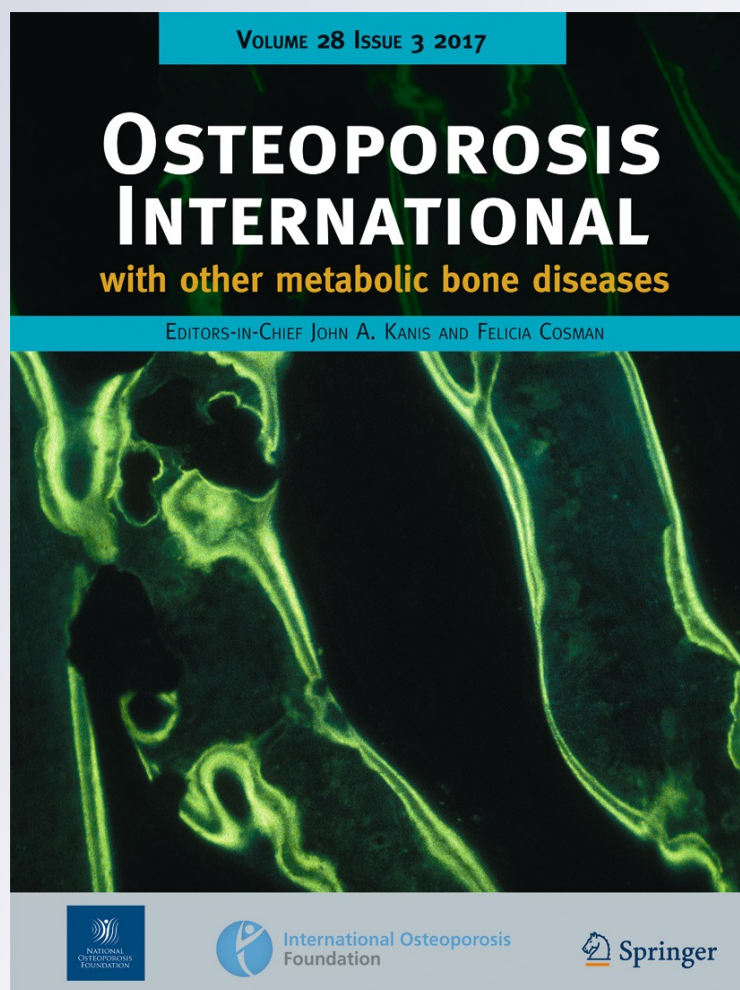
*Public health impact and economic evaluation of vitamin D-fortified dairy products for fracture prevention in France*

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**Osteoporosis International**  
With other metabolic bone diseases

ISSN 0937-941X  
Volume 28  
Number 3

Osteoporos Int (2017) 28:833-840  
DOI 10.1007/s00198-016-3786-1



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# Public health impact and economic evaluation of vitamin D-fortified dairy products for fracture prevention in France

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Received: 23 June 2016 / Accepted: 22 September 2016 / Published online: 18 October 2016  
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## Abstract

**Summary** The recommended intake of vitamin D-fortified dairy products can substantially decrease the burden of osteoporotic fractures and seems an economically beneficial strategy in the general French population aged over 60 years.

**Introduction** This study aims to assess the public health and economic impact of vitamin D-fortified dairy products in the general French population aged over 60 years.

**Methods** We estimated the lifetime health impacts expressed in number of fractures prevented, life years gained, and quality-adjusted life years (QALY) gained of the recommended intake of dairy products in the general French population over 60 years for 1 year (2015). A validated microsimulation model was used to simulate three age cohorts for both women and men (60–69, 70–79, and >80 years). The incremental cost per QALY gained of vitamin D-fortified dairy products compared to the absence of appropriate intake was estimated in different populations, assuming the cost of two dairy products per day in base case.

**Results** The total lifetime number of fractures decreased by 64,932 for the recommended intake of dairy products in the general population over 60 years, of which 46,472 and 18,460 occurred in women and men, respectively. In particular, 15,087 and 4413 hip fractures could be prevented in women and men. Vitamin D-fortified dairy products also resulted in 32,569 QALYs and 29,169 life years gained. The cost per QALY gained of appropriate dairy intake was estimated at €58,244 and fall below a threshold of €30,000 per QALY gained in women over 70 years and in men over 80 years.

**Conclusion** Vitamin D-fortified dairy products have the potential to substantially reduce the burden of osteoporotic fractures in France and seem an economically beneficial strategy, especially in the general population aged above 70 years.

**Keywords** Cost-effectiveness · Dairy products · Fractures · France · Public health

## Introduction

Osteoporotic fractures represent a major public health problem that leads to increased morbidity, mortality, and health care costs [1]. In France, it was estimated that 50,215 and 15,482 hip fractures occurred in the year 2013 in women and men, respectively [2]. In another report prepared in collaboration between the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA), the economic burden of incident and previous fragility fractures was estimated at €4853 million in France and fractures accounted for 139,400 quality-adjusted life years (QALYs) lost in 2010 [1].

Calcium and vitamin D are crucial for bone health and fracture prevention. A European consensus group recommends adequate vitamin D intake of 800 IU/day and calcium

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intake of 1000 mg per day [3]. Several studies reported a high prevalence of vitamin D insufficiency and low dietary calcium in many elderly men and women [4, 5]. In France, only 20 % of women consumed  $\geq 1000$  mg of calcium per day [6] and the prevalence of vitamin D inadequacy is  $>85$  % in women with osteoporosis or osteopenia aged over 50 years as well as in elderly subjects above 80 years [5, 7]. Several studies have reported that the current intake of calcium and vitamin D is far from optimal in France [6, 8–10]. By example, one large scale study estimated that, respectively, 73.9 and 86.5 % of elderly women have low dietary intakes of vitamin D and low dietary calcium intakes [8]. It is therefore important to adequately supplement elderly patients with calcium and vitamin D [3, 11]. The use of dietary sources of calcium has been recommended as the preferred option by the European guidance for the diagnosis and management of osteoporosis [12]. The French National Nutrition and Health Program recommends the consumption of three dairy product servings/day for adults (3 to 4 for over 55-year-olds) but only 29 % of French adults meet this recommendation [13].

Assessing the public health and economic impact of the recommended intake of dairy products and vitamin D would be important to help policy makers in evaluating and making decisions about preventive programs, especially in the context of limited health care resources. To date, relatively few studies have assessed the public health and economic impact of vitamin D-fortified dairy products given to the general elderly population [14–17]. These studies suggest the public health and economic value of fortified dairy products. To our knowledge, no study has been conducted to assess the public health and economic impact of vitamin D-fortified dairy products for fracture prevention in France.

This study therefore aimed to estimate the public health and economic impact of dairy products supplemented with vitamin D in the general population aged over 60 years in France. Specifically, we estimated the impact of the recommended intake of fortified dairy products on the number of fractures prevented, on life years gained, on gained, and evaluated the cost-effectiveness of fortified dairy products compared with the absence of appropriate intake in terms of cost per QALY gained.

## Methods

We used a previously validated Markov microsimulation model [18] to estimate the public health and economic impact of the recommended intake of vitamin D-fortified dairy products in France compared to the absence of appropriate intake. The model simulates over lifetime the number of fractures (hip, clinical vertebral, wrist, other and all), life years, QALY, and total health care costs. The more recent version of the model with a 6-month time horizon was used in this

study [17, 19] and was adjusted to the French setting. In a Markov model, patients transit between different health states (no fracture, fractures, post fracture, and death) according to transition probabilities. Description of the model can be found in previous publications (9, 10).

Analyses were conducted in the general population in France aged over 60 years, including women and men. In both genders, three age cohorts (60–69 years, 70–79 years, 80+) were used to estimate outcomes using the software TreeAge Pro 2011 (TreeAge Pro Inc., Williamston, MA). For each cohort, we simulated 1,000,000 microsimulations. The base year of the analysis was 2015. We therefore estimated the impact of vitamin D-fortified dairy products to all individuals for 1 year (2015 base case) and estimated the lifetime effect of this intervention. Based on the distribution of the population in each cohort that was obtained from the National Institute of Statistics and Economic Studies (INSEE) [20] (see Table 1), we then calculated using an Excel sheet, the total costs, and outcomes in the general French population aged above 60 years. Projections for the years 2025 and 2050 were also done using populations projections from INSEE [21] to evaluate the effects of demographic changes on the benefits of the strategy.

Incidence of hip fractures in the general population was derived from the recent study of Briot et al. [2] using data from the year 2013 (see Table 2). As no data for the incidence of other osteoporotic fractures (i.e., clinical vertebral, wrist, and other fractures) are available in France, we applied the age-specific ratio incidence from other countries in line with previous publications [1]. In addition, the model assumed an increased risk of fracture for individuals who had a prior fracture at the same location [18]. Mortality data for the general population were derived from INSEE for the years 2011–2013 [22]. According to data from a meta-analysis [23], hip fractures increased female (male) death probabilities by 4.53 (5.75) in the first 6 months following the fracture, by 1.75 (2.31) in the period 6–12 months, and by 1.78 (1.69) in subsequent years. The same impact was assumed after hip and clinical vertebral fractures. We conservatively assumed that only 25 % of the excess mortality following a hip or vertebral fracture could be directly or indirectly attributable to the fractures themselves. Utility values in the general French population (used for patients without fracture) was estimated at 0.766 [24]. Relative reductions due to fractures in the year following the fracture and in subsequent years were derived from a systematic review [25].

The health care perspective was used for the cost estimation. As productivity losses are limited in patients over 60 years, the perspective is quasi-societal. The cost of hip and wrist fractures was derived from the study of Boue et al. [26]. The cost of clinical vertebral fracture was derived from a previous cost-effectiveness analysis in France [27]. The cost of other fractures was assumed to represent 17.6 %



**Table 1** Population estimates (2015) and projections for 2025 and 2050 in the general French population aged over 60 years

French population (age in years)	Women			Men		
	2015	2025	2050	2015	2025	2050
60–69	3,961,492	4,171,501	4,038,239	3,614,450	3,783,468	3,921,701
70–79	2,507,933	3,663,128	3,786,400	2,036,842	3,045,407	3,321,749
≥80	2,458,810	2,679,558	4,832,570	1,324,216	1,525,294	3,109,529

from the cost of hip fracture, in line with Melton et al. [28]. All costs were expressed in €2015 using the national price index (health index) and a discount rate of 3 % was used for both costs and outcomes. The costs of fractures for the year 2015 were thus estimated at €11,970, €6201, €2124, and €2093 for hip, clinical vertebral, wrist, and other fractures, respectively. Hip fractures are also associated with long-term costs. These long-term costs were based on the proportion of patients being institutionalized after the fracture. Based on the study of Drame et al. [29], 20.1 % of patients with a hip fracture were institutionalized after a hip fracture in French population aged above 75 years. For patients aged between 60 and 74 years, we conservatively assumed that 10 % of patients were institutionalized after a hip fracture in line with international studies [1]. The yearly costs of nursing home were estimated at €37,255 based on national data.

The effect of adequate intake of calcium and vitamin D was derived from a recent Cochrane Review [30]. Based on this review, the fracture incidence reduction of vitamin D and calcium intervention was 16, 14, 11, and 11 % for hip fracture, clinical vertebral, wrist, and other fractures, respectively. These estimations are slightly more conservative than those used in previous economic evaluations of calcium and vitamin D [14, 17] (estimated at 18, 13, 20, and 20 %, respectively). In the model, people only received fortified dairy products for 1 year (2015 in base case), and no further effect was assumed after the year of treatment. The model has however a lifetime horizon to capture the long-term benefits of preventing fractures in the year of the intake of fortified dairy products.

The cost of one vitamin D-fortified dairy product was estimated at €0.27 in France based on the prices of two leading industry suppliers from three French cities for vitamin D-enriched milk and yogurt (on the date of 20/01/2016). Based on current consumption of calcium and vitamin D in France

and European recommendation on adequate levels [3, 6], two vitamin D fortified dairy products per day are needed to achieve optimal intake of calcium and vitamin D. We therefore assumed the price of two dairy products per day in the base case for the economic analysis.

### Presentation of results and sensitivity analyses

We estimated the lifetime number of fractures prevented (per type), life years gained, and QALY gained of recommended dairy intake versus absence of appropriate intake for the year 2015. Data are presented for the overall population aged over 60 years as well as per age group and gender. Incremental cost-effective ratios (ICERs) were estimated for the recommended intake of fortified dairy products versus usual care. ICERs are defined as the differences in costs between alternatives divided by their differences in outcomes (expressed in QALYs). An ICER represents therefore, the cost per QALY gained of recommended intake of fortified dairy products versus usual care. Projections for the years 2025 and 2050 were also conducted to evaluate the effects of demographic changes on the potential benefits of the strategy.

We conducted 11 additional one-way sensitivity analyses (SA) to assess the impact of parameters on the lifetime number of fractures prevented and QALY gained, and on the cost per QALY gained of the recommended dairy intake. SA1: all fracture risk +25 %; SA2: all fracture risk –25 %; SA3: therapy efficacy +25 %; SA4: therapy efficacy –25 %; SA5: therapy cost +50 % (three dairy products per day); SA6: therapy cost –50 % (one dairy product per day); SA7: 80 % intake of dairy products based on current levels of calcium and vitamin D intake in France [8]; SA8: 50 % intake of dairy products; SA9: therapy cost for all patients but benefits for 75 %; SA10: no increased fracture risk after previous fractures; SA11: an

**Table 2** Fracture incidence in the general French population aged over 60 years

Fracture incidence (per 1000) (age in years)	Women				Men			
	Hip	CV	Wrist	Others	Hip	CV	Wrist	Others
60–74	0.117	0.181	0.313	0.394	0.074	0.135	0.100	0.528
75–84	0.689	0.551	0.551	1.311	0.323	0.298	0.077	0.861
≥85	2.312	1.087	0.986	3.884	1.255	0.842	0.230	3.682

CV clinical vertebral

**Table 3** Projected health impact of vitamin D-fortified dairy products in the general population aged over 60 years in France in the year 2015

	Women				Men			
	60–69	70–79	80+	All (≥60 years)	60–69	70–79	80+	All (≥60 years)
Lifetime fractures saved								
Hip	844	3729	10,514	15,087	437	1198	2778	4413
CV	1169	2087	4197	7452	846	851	1326	3023
Wrist	1490	1959	2646	6094	351	196	491	1037
Other	2199	4284	11,357	17,839	2440	2047	5499	9986
Total	5701	12,058	28,714	46,472	4073	4292	10,094	18,460
QALY gained	4474	6919	11,674	23,067	2958	2795	3748	9502
Life years gained	4946	5177	9256	19,378	3889	2693	3209	9791

CV clinical vertebral, QALY quality-adjusted life years, Y years

additional 8 % costs for marketing and education costs to raise consumer awareness and ensure their acceptance, based on a German study estimate [15]. Results of the sensitivity analyses are presented in tornado diagrams.

## Results

Table 3 summarizes the projected health impact of the recommended intake of fortified dairy products compared to the absence of appropriate intake for women and men aged over 60 years in 2015 in France. The total lifetime number of fractures was reduced by 64,932 for the recommended intake of dairy products in the general population over 65 years, of which 46,473 and 18,460 occurred in women and men, respectively. In particular, 15,087 and 4413 hip fractures could be prevented in women and men. The intake of dairy products resulted in a QALY gained of 32,569 and a gain of 29,169 life years. Most of the benefits of fortified dairy products occurred in women and men aged over 80 years, respectively, 62 and 55 % of fractures prevented can be found in these populations. Results of the sensitivity analysis assuming an adherence level of 82 % can be found in online supplement.

In Table 4, projections of the health impact of fortified dairy products for the years 2025 and 2050 are presented. Taken into account demographic changes only, we estimated that 19 and 78 % more fractures could be prevented with appropriate intake of fortified dairy products in the years 2025 and 2050, respectively.

The total cost impact of the two extra vitamin D fortified dairy products/day compared with usual intake was estimated for the year 2015 at €1555 million in the general population aged over 60 years. The cost of dairy products was estimated at €2570 million and €1014 million were saved because of less fractures resulting from intervention efficacy. Overall,

39 % of the cost of dairy products would then be compensated by saved costs resulting from fewer fractures.

The incremental cost-effectiveness ratio (expressed in cost per QALY gained) of appropriate intake of fortified dairy products compared with the absence of appropriate intake is reported in Table 5. The ICER is estimated at €58,244 per QALY gained in the French population aged over 60 years. The ICER was €38,526 and €106,113 in women and men, respectively. The ICER was below the threshold of €30,000 per QALY gained in women aged above 70 years and in men aged over 80 years. Projections of cost-effectiveness suggest that the ICER in the general population aged above 60 years would decrease to €55,953 in the year 2025 and to €43,620 in 2050. Sensitivity analyses assuming the cost of one and three dairy products per day are also included in Table 5. One fortified dairy product per day is highly cost-effective in the French general population aged above 60 years (ICER of €10,121 per QALY gained).

**Table 4** Projection of health impact of dairy products in the general population aged over 60 years in France for the years 2025 and 2050

	Women			Men		
	2015	2025	2050	2015	2025	2050
Lifetime fractures prevented						
Hip	15,087	17,793	27,155	4413	5449	8952
CV	7452	8852	12,591	3023	3685	5419
Wrist	6094	7313	9675	1037	1225	1853
Other	17,839	20,949	31,030	9986	11,949	18,899
Total	46,472	54,907	80,451	18,460	22,308	35,123
QALY gained	23,067	27,539	37,951	9502	11,594	16,570
Life years gained	19,378	22,856	31,049	9791	11,794	16,146

CV clinical vertebral, QALY quality-adjusted life years

**Table 5** Cost-effectiveness (expressed in cost per QALY gained) of the recommended intake of vitamin D-fortified dairy products compared to usual care in the French general population aged over 60 years

Population	One dairy product per day	Two dairy products per day	Three dairy products per day
Overall	€10,121	€58,244	€106,367
Women			
60–69	€67,640	€155,006	€242,272
70–79	Cost-saving <sup>a</sup>	€24,997	€60,719
80+	Cost-saving	€1907	€22,663
All ages	€382	€38,526	€76,670
Men			
60–69	€97,772	€218,176	€338,581
70–79	€20,868	€92,676	€164,484
80+	Cost-saving	€27,683	€62,501
All ages	€33,766	€106,113	€178,460
Projections (overall)			
2025	€8436	€55,953	€103,470
2050	€2028	€43,620	€85,212

<sup>a</sup> Cost-saving means that intervention costs are lower than saved costs resulting from less fractures

One-way sensitivity analyses are included as tornado diagrams in Fig. 1. The largest change in terms of public health impact (number of fractures prevented or QALYs gained) occurred when reducing dairy products intake (to 50 %) followed by decreasing therapy efficacy or all fracture risk by 25 % (Fig. 1a, b). The cost-effectiveness of the recommended dairy intake is strongly influenced by the cost of fortified dairy products, the effectiveness of calcium and vitamin D, and the fracture risk of the population.

## Discussion

Our study suggests that an adequate intake of calcium and vitamin D by the administration of vitamin D fortified dairy products could substantially reduce the burden of osteoporotic fractures in France. We estimated that the recommended intake of fortified dairy products in the year 2015 would lead to a lifetime decrease of 64,932 fractures including 19,500 hip fractures. Given 65,697 hip fractures occurred in the year 2013 in France [2], the benefit of fortified dairy products is therefore substantial. Projections suggest that the number of prevented fractures through appropriate intake of dairy products could even increase by 78 % in the year 2050 taken into account demographic changes.

In addition, we estimated the cost-effectiveness of the recommended intake of vitamin D-fortified dairy products compared to the absence of dietary intake. To draw a conclusion about the cost-effectiveness, the cost per QALY gained has to be compared with a cost-effectiveness threshold. This threshold represents the maximum amount that the decision makers are willing to pay. In France, as in most countries, there is no consensus on cost-effectiveness. In the overall French population aged 60 years and over, we found a cost per QALY

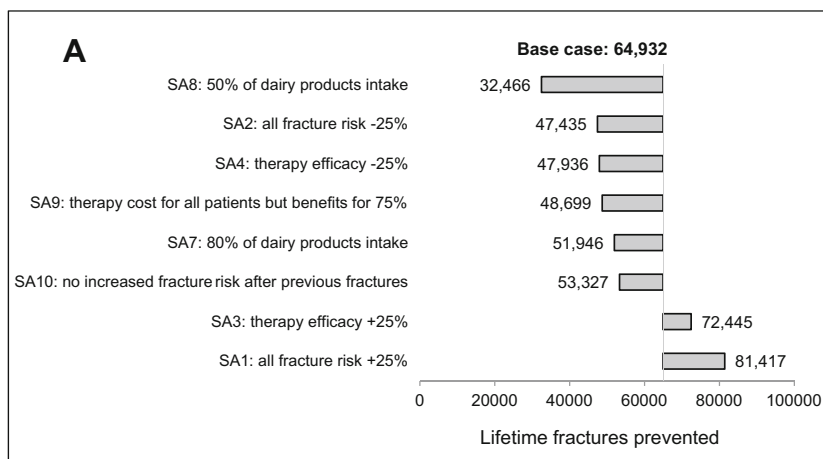
gained of €58,244, in the range of commonly accepted threshold for cost-effectiveness. The intake of fortified dairy products becomes highly cost-effective (cost per QALY <€30,000) in women over 70 years and in men over 80 years.

Similarly, Ethgen et al. also showed that the intake of dairy products is cost-effective in the general population over 70 years in Belgium [31]. Our study is more conservative as we did not incorporate any treatment effect after the year of the intake of fortified dairy products. A large public health benefit expressed in life years and fractures prevented, was also estimated in another Belgian study [14]. However, a different approach was used to assess the public health burden making comparison with our study difficult. In a recent German study, Sandman et al. [15] suggested that the implementation of dietary vitamin D and calcium food-fortification program in the German population aged 65 years and older would even lead to annual net cost savings. Lower cost for dietary products was used in this study which could explain the more positive benefit of the intervention.

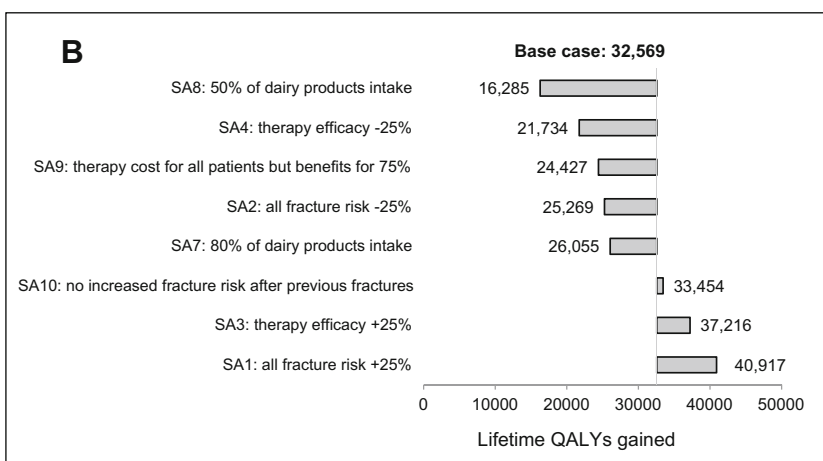
Our study therefore suggests that an adequate intake of calcium and vitamin D by the administration of vitamin D-fortified dairy products could lead to a substantial decrease in the burden of osteoporotic fractures and could be justified from an economic perspective in women over 70 years and in men over 80 years (assuming a threshold of €30,000 per QALY gained). Decision makers should be aware of the benefits of calcium and vitamin D and could be interested to implement programs to increase the intake of dairy products. Such programs have already been implemented in some countries [32, 33]. Clinicians should also take actions to improve the consumption of fortified dairy products by their patients.

There are some potential limitations to our study. First, our study was limited to the potential benefits of calcium and vitamin D on fracture prevention and we could have

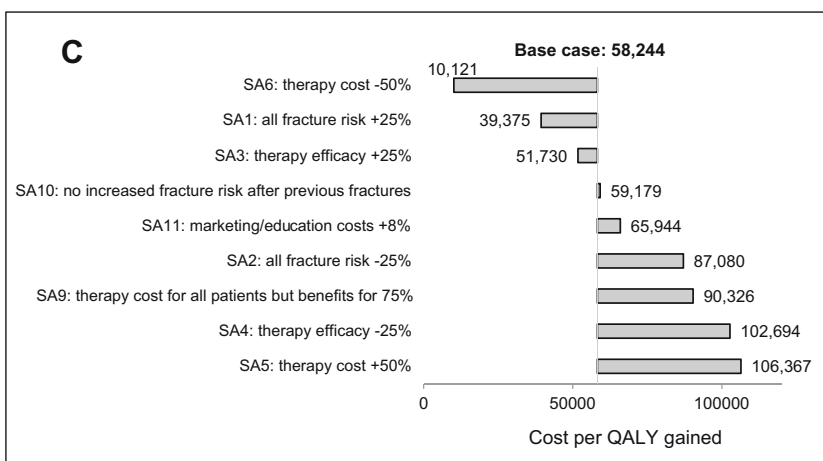
**Fig. 1** Tornado diagrams for one-way sensitivity analyses on the health impact expressed in lifetime number of fractures prevented (Fig. 1a), in QALYs gained (Fig. 1b), and on the cost-effectiveness (expressed in cost per QALY gained) of vitamin D-fortified dairy products (Fig. 1c) in the general population aged over 60 years in France in the year 2015. SA5, SA6, and SA11 have no impact on the lifetime number of fractures prevented



SA5, SA6 and SA11 have no impact on the lifetime number of fractures prevented



SA5, SA6 and SA11 have no impact on the lifetime QALYs gained



SA7 and SA8 have no impact on the cost per QALYs gained

underestimated the benefits of the intervention. There are other potential benefits of calcium and vitamin D including the

reduction on the risk for breast cancer in premenopausal women and colon cancer in older women [34]. Dairy products are



also rich in proteins which could also lead to extra health benefits [35]. A meta-analysis also indicated that vitamin D may have a small beneficial effect on cardiovascular risk and mortality [36]. On the other hand, we did not incorporate any adverse events although the risk seems limited [37]. Second, a few patients already have an adequate level of calcium and vitamin D through nutrients [5, 6]. On the opposite, the benefits for some patients with large insufficiency in vitamin D and/or calcium could be even larger than the assumed effect. Having an adequate level of calcium and vitamin D could also lead to higher benefits of pharmacological treatment for osteoporosis [14]. We could reasonably assume that all these effects could compensate each other. Third, we did not specifically incorporate adherence to fortified dairy products in the analysis. Little is known about adherence to fortified dairy products and how this could affect intervention efficacy. In sensitivity analyses, we assumed that only 80 or 50 % of patients would be willing to consume fortified dairy products. Further studies are needed to assess adherence to fortified dairy products and willingness of the French population to consume fortified dairy products. Lastly, the effect of calcium and vitamin D on fracture risk reduction was derived from a Cochrane Review that was based on all trials about calcium and vitamin D compounds [30]. Further studies are needed to assess the effects of calcium and vitamin D by the administration of fortified dairy products.

In conclusion, this study suggests that the intake of vitamin D fortified dairy products have the potential to substantially reduce the burden of osteoporotic fractures and could be an economically beneficial strategy in France, especially in the general population aged above 70 years.

**Acknowledgments** The Department of Public Health, Epidemiology and Health Economics of the University of Liege has received an unrestricted educational grant from CNIEL (Paris, France). The funding agreement ensured the authors' independence in designing the study, interpreting the data, and writing and publishing the report. We thank the Prince Mutaib Bin Abdullah Chair for Biomarkers of Osteoporosis and Deanship of Scientific Research, King Saud University for their support.

#### Compliance with ethical standards

**Conflicts of interest** Jean-Yves Reginster has received research grant and/or consulting fees from Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed-Takeda, NPS, IBSA Genevrier, Theramex, UCB, Asahi Kasei, Endocyte, Merck Sharp and Dohme, Rottapharm, Teijin, Teva, Analis, NovoNordisk, Ebewee Pharma, Zodiac, Danone, Will Pharma, Meda, Bristol Myers Squibb, Pfizer, Organon, Therabel, Boehringer, Chiltern, Galapagos. Patrice Fardellone has received consulting fees from the following: Amgen, Candia, Danone, Expanscience, Lilly, Roche-Chugai, Pfizer, and UCB. Mickael Hiligsmann, Nansa Burlet, and Nasser Al-Daghri have no relevant competing interests to declare.

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