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ANALYSIS

Web of industry, advocacy, and academia in the management of osteoporosis

Calcium and vitamin D supplementation continue to be recommended to prevent and treat osteoporosis despite evidence of lack of benefit, say **Andrew Grey** and **Mark Bolland**. They **examine** why change is difficult and call for advocacy organisations, academics, and specialist societies to abandon industry ties

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For many years, recommendations for prevention and treatment of osteoporosis have included increasing calcium intake (by diet or supplements) and use of vitamin D supplements. Since the average dietary calcium intake in most countries is much less than that recommended by guidelines (table 1⇓), many older people are advised to take calcium supplements to prevent osteoporosis. The recommendations have been implemented successfully: over half of older Americans take calcium and vitamin D supplements, either prescribed or over the counter, and bone health is the most common specific motivation for use of nutritional supplements.[1 2] However, this behaviour does not reflect evidence that has emerged since 2002 that such supplements do not reduce the risk of fracture and may result in harm. Guideline bodies also continue to recommend calcium and vitamin D supplements. Here, we argue that change is made difficult by a complex web of interactions between industry, advocacy organisations, and academia.

Evidence on calcium and vitamin D

The first consensus statement on osteoporosis in 1984 recommended a daily calcium intake of 1500 mg in postmenopausal women, based on short term whole body calcium balance studies.[3 4] Later, use of vitamin D supplements in older adults was recommended by an osteoporosis consensus development panel based on extrapolation from a trial conducted in frail, very elderly, institutionalised women to the general population.[5 6] Enthusiasm for calcium and vitamin D supplementation was fuelled by a small randomised trial that reported a reduced incidence of fracture[7] and studies that defined adequate levels of vitamin D using the level of parathyroid hormone.[8 9] By the early 2000s, routine calcium and vitamin D supplementation to prevent or treat osteoporosis in older adults was embedded in clinical practice.

The main aim of managing osteoporosis is to prevent fracture. From 2002, evidence from randomised trials began to challenge the notion that calcium or vitamin D supplements alone or in combination safely reduce fracture risk. By the end of 2010, 14 large (>1000 participants) randomised trials of calcium supplements, vitamin D supplements, or their combination had been published: three reported reduction in fracture risk, nine no effect, and two increased fracture risk (figure⇓). Among 24 small randomised trials, 21 found no effect. Meta-analyses of these trials, when analysed by intention to treat, report either no effect on fracture risk[10 11] or marginal risk reduction of doubtful clinical importance.[12 13] A trial sequential analysis reported last year that sufficient evidence is available to conclude that vitamin D with or without calcium does not reduce total fracture risk by >10% and that additional trials are unlikely to alter that finding.[11] Randomised trials of the effect of food sources of calcium have not been conducted, but observational evidence does not suggest that increasing dietary calcium intake reduces fracture risk.[14-16]

Evidence for harms also emerged, including hospital admission for gastrointestinal symptoms, kidney stones, falls, hip fracture, myocardial infarction, and stroke (table 2⇓). Among older adults living independently, the number needed to harm for vascular events (178) is less than the number needed to treat to prevent a fracture (302).[17]

We conclude that increased calcium and vitamin D intake should not have been recommended for older adults living independently after 2007, a view consistent with the conclusion of the 2009 Cochrane review.[18] However, many guidelines published since then recommend increasing calcium intake (to 1000-1200 mg/day) or use of vitamin D supplements (600-2000 IU/day) for managing osteoporosis (table 1⇓). An exception is the United States Preventive Services Task Force, which

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recommended against calcium and vitamin D supplementation for primary fracture prevention in 2013.[19]

Several therapies previously recommended for osteoporosis (oestrogen, calcitonin, fluoride) have been discarded because of evidence of lack of efficacy or important harm. So why are calcium and vitamin D supplements still widely recommended? One possible explanation is vested interests of industry, advocacy organisations, and academia. We searched the websites of key commercial and advocacy organisations and specialist societies to determine the extent of these interests.

Commercial value to industry

Calcium and vitamin D supplements are very profitable. Global annual sales of calcium supplements in 2013 were about $6bn (£4bn; €5bn),[w1] and those of vitamin D in the US in 2012 were $748m.[w2] Companies that market foods rich in calcium or vitamin D also profit from the notion that these nutrients prevent osteoporosis. Notable examples include Fonterra, whose $NZ4bn (£2bn; €3bn; $3bn) annual sales in Asia include those of its calcium enriched milk products marketed for optimal bone health,[w3] and Danone, whose annual sales of fresh dairy products are around €12bn (£9bn; $13bn), including products marketed as promoting bone health because they contain calcium and vitamin D.[w4]

Other industries benefit from enthusiasm for use of supplements for osteoporosis. Measurement of serum 25-hydroxyvitamin D has become widely used,[20 21] benefiting both the manufacturers of assay kits and the laboratories that perform the tests. The commercial rewards are substantial— annual costs of vitamin D testing in Australia increased from $A1m (£500 000; €700 000; $800 000) in 2001 to $A96m in 2010.[21]

Industry and advocacy organisations

The US National Osteoporosis Foundation (NOF) and the Europe based International Osteoporosis Foundation (IOF) are highly influential advocacy organisations. Both state their aim as improving patient outcomes, but their objectivity may be compromised by the influence of a range of commercial sponsors, including companies that market supplements, dairy products, and nutrition related laboratory tests.[w5 w6] In their drive to attract corporate sponsorship, the IOF and NOF emphasise their academic and scientific strengths and global influence, and offer the opportunity for corporate members to influence the strategic direction of the organisation at both formal and informal levels.[w7 w8]

Twelve of the 22 NOF corporate sponsors and 14 of the 25 IOF corporate sponsors are active in nutrition related commercial enterprises (table 3⇓). According to the NOF website its corporate advisory roundtable is a "high-level corporate advisory body to NOF's Board of Trustees" whose "current programs are focused on the importance of calcium and vitamin D in prevention and treatment of osteoporosis."[w7] Members include supplements manufacturers, companies that produce vitamin D test kits, and the Council for Responsible Nutrition, which describes itself as the "leading trade association representing dietary supplement manufacturers and ingredient suppliers."[w9]

After evidence accrued that calcium and vitamin D do not safely reduce fracture risk, the nutrition industry continued to partner osteoporosis advocacy organisations to promote their widespread use. For example, in 2010 DSM, "the world's largest manufacturer of vitamin D_3," [w10] partnered the IOF to produce a global vitamin D map, the launch of which was accompanied by claims that vitamin D deficiency is present throughout Europe and calls for more supplementation of older adults.[w11] Fonterra became the IOF Asia Pacific Regional Nutrition Partner in 2010 and has aligned with, and financially supported, osteoporosis advocacy groups throughout Asia.[w12 w13] In 2014, the IOF partnered Danone to promote the bone benefits of dairy products,[w14] and the NOF aligned with Bayer HealthCare to promote use of Bayer's calcium supplement for skeletal health of older women.[w15]

Responses to unfavourable evidence

The NOF and IOF have not changed their positions to reflect the accumulating evidence of lack of benefit of calcium and vitamin D for osteoporosis. In response to the conclusion by the US Preventive Services Task Force panel in 2013 that neither calcium nor vitamin D supplements are necessary in older adults, both organisations maintained that each intervention is an important part of fracture prevention, and the NOF expressed concern that it might lead to fewer people getting sufficient intakes of each compound.[w16]

The Council for Responsible Nutrition (CRN) advocates for use of supplements even when clinical trial evidence shows ineffectiveness or harm.[22] For example, in response to a 2010 meta-analysis that reported adverse cardiovascular outcomes with calcium supplements,[23] a press release stated that the work "should not cause consumers to doubt the value of calcium supplements for maintaining bone health."[w17] In 2011, responding to further evidence of cardiovascular harms from calcium, the council noted on its website that the finding "has the potential to negatively influence consumers' views of the importance of calcium" and urged member companies for whom "calcium is key to your business" to financially support an initiative to counter "potentially unwarranted negative media coverage" and assist the production and dissemination of a critical manuscript[24] by a CRN convened working group that included CRN employees.[25] To implement this initiative, CRN partnered the NOF to develop "educational strategies and communication tactics," that included hosting a webinar for pharmacists and nurse practitioners on "the updated recommendations and research of calcium and vitamin D."[w18]

Other industry sponsored advocacy organisations have failed to acknowledge the unfavourable evidence. The news section of the website of the Vitamin D Council does not mention the recent meta-analyses of randomised trials that reported no health benefits of vitamin D supplements,[11 26 27] while less rigorous research findings that encourage vitamin D testing and use are enthusiastically endorsed.[w19]

Industry, advocacy, and academia

The nutrition industry influences research that affects its products. It funds research, presumably hoping that the outcomes will support use of its products,[28 29 w20] and sponsors meetings at which prominent academic speakers advocate nutritional supplements.[30 w20] Financial involvement of the nutrition industry in calcium and vitamin D publications has been inconsistently acknowledged. For example, in publications about vitamin D coauthored with bone nutrition academics, employees of the CRN[31] and DSM[30] acknowledged their affiliations but declared no financial conflicts of interest. In addition, prominent academics wrote manuscripts about vitamin D[30 32-34] and calcium[24] without disclosing relevant conflicts of interest, including receiving money for research support, participation in speakers bureaus, and payments for consultancies and writing manuscripts.[w21] Other groups of academics that are sponsored by companies that market nutritional supplements, dairy foods,

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or vitamin D assay kits, such as the Belgian Bone Club[w22] and the International Institute for Nutrition and Bone Health,[w23] formulate "consensus" documents and publish manuscripts that endorse nutritional interventions without always acknowledging,[35 36] or incompletely acknowledging,[37] their commercial conflicts of interest.

More insidiously, industry supported advocacy organisations, which may have prominent academics on their scientific advisory committees,[w24] commission or support research that continues to promote use of nutritional interventions. A notable example is a 2013 reanalysis of hip fracture data from the Women's Health Initiative trial of calcium and vitamin D that emphasised the positive result among the subgroup of participants exposed for over five years (hazard ratio 0.62, 95% confidence interval 0.38 to 1.00) when no effect was present overall (0.86, 0.62 to 1.20).[38 w25] The NOF promoted the result as "underscoring the well-documented benefits of calcium."[w26] In a second example, the Australian Self Medication Industry commissioned and cofunded a systematic review of calcium supplements and promoted its results.[w27] The roles of industry in the research were not disclosed in the original publication and an amendment published five years later still did not mention them.[w28] The review concluded, "Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 years or older,"[12] but a contemporaneous analysis of calcium studies reported that "Pooled results from randomized controlled trials show no reduction in hip fracture risk with calcium supplementation, and an increased risk is possible. For any nonvertebral fractures, there was a neutral effect in the randomized trials."[14]

The National Bone Health Alliance—a public-private partnership established in 2010 that is an offshoot of the NOF—recently recommended broadening the diagnostic criteria for osteoporosis to include people whose 10 year hip fracture risk exceeds 3%.[39] The threshold is derived from a computer modelled cost effectiveness analysis[40] conducted by the NOF that has not been evaluated in clinical studies. Its application would lead to recommendations for treatment in 50% and 86% of American men and women aged >75 years, respectively.[41] Most of those treated would not benefit because the number needed to treat to prevent a hip fracture during five years of bisphosphonate therapy in a population with a 10 year hip fracture risk of 3% is 167.[42] The 3% intervention threshold has been integrated into the US version of a commonly used fracture risk algorithm,[w28] the development of which was also supported by the NOF, the IOF, and several industry sponsors, including those marketing nutritional supplements.[43 44] Recommendations to increase the use of drugs to reduce fracture risk will also increase use of calcium and vitamin D supplements since these are widely recommended as adjunctive treatments with antiresorptive drugs, even though evidence for synergistic effects on fracture risk is lacking.[45]

Academics in specialist societies play prominent roles in medical education and advocacy. Concern about commercial influences prompted recommendations from academics in 2009 to minimise industry funding of societies in all specialties and remove commercial conflicts of interest from senior positions within societies and the committees responsible for development of guidelines and scientific meeting programmes.[46] In osteoporosis, the nutrition industry features prominently among corporate sponsors of specialist societies and their scientific meetings (table 3⇓). However, the websites of those societies do not give conflict of interest statements from academic society staff in leadership positions. In three recent publications of position statements coauthored by bone specialist society academics, 43 authors declared a total of 270 financial conflicts of interests.[47-49]

Setting aside finances, academic leaders may also have academic conflicts of interest. For example, their career development may be enhanced by the persistence of beliefs that nutritional supplements benefit the skeleton. Such conflicts of interest may have influenced the Endocrine Society's endorsement of widespread moderate dose vitamin D supplementation in contrast with the Institute of Medicine (IOM), which recommended low level supplementation for older adults, and the Preventive Services Task Force, which advised against vitamin D supplementation.[19 49 w29] Among the eight Endocrine Society guideline authors, the median (range) proportion of their publications that had vitamin D or calcium as a major subject MESH term was 27% (1-70). The corresponding proportions for the 15 IOM guideline authors and 14 task force guideline authors were 10% (0.6-70) and 0% (0-2.4), respectively.

Winners and losers

The interactions among the nutrition industry, advocacy organisations, and academia are complex. Each party benefits. Industry gains scientific credibility, which protects or enhances sales of its products, and indirect marketing through advocacy groups. Advocacy organisations and specialist societies gain funds to support their existence. Academics gain by maintenance of their status and by obtaining access to research funds and career enhancing publications and presentations. The party that may lose, and be harmed, is the public. Failure to reverse inappropriate practice leads to overtreatment,[50 51] systematic waste of healthcare resources, unnecessary costs for patients, and missed opportunities for application of interventions with proved efficacy. Ultimately, the cost is erosion of trust in the medical system.

Improving transparency of the interactions between industry, academia, and advocacy organisations is desirable but reducing those interactions is more so. The emerging requirements that drug companies declare payments to health practitioners should be broadened to include supplements and food manufacturers. Advocacy organisations and specialist societies should eschew corporate sponsorship, and academics should not engage with advocacy organisations until it is clear that such commercial ties have been severed.

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Key messages

- Calcium and vitamin D are highly profitable treatments that are widely recommended for osteoporosis despite increasing evidence contradicting the practice
- Industry and its lobby groups fund and influence the activities and policies of osteoporosis advocacy organisations
- Academia, including specialist societies, have both commercial and academic conflicts of interest in the nutrition osteoporosis field
- Disentangling industry from academia might improve the translation of evidence into practice

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Tables

Table 1| Guideline recommendations on calcium and vitamin D intake for prevention and treatment of osteoporosis

Source*	Year	Recommendations for daily intake for older adults	
		Calcium (mg)	Vitamin D (IU)
NIH Consensus Conference	1984	1000-1500	—
Consensus Conference†:	1993		
Premenopausal women		1000	
Postmenopausal women		1500	
European Foundation for Osteoporosis and Bone Disease‡	1997	1000-1500	400-800
Institute of Medicine	1997		
Adults 51-70 years		1200	400
Adults >70 years		1200	600
National Osteoporosis Foundation	1999	≥1200	400-800
Osteoporosis Society of Canada	2002	1500	800
European Society for Economic Aspects of Osteoporosis and Osteoarthritis	2008	≥1000	800
National Osteoporosis Foundation	2008	≥1200	800-1000
UK National Osteoporosis Guidelines Group	2009	≥1000	800
Osteoporosis Canada	2010	1200	400-1000
Institute of Medicine	2011		
Men 50-70 years		1000	600
Women 50-70 years		1200	600
Adults >70 years		1200	800
Endocrine Society	2011	—	1500-2000
American Association of Clinical Endocrinologists	2012	1200	800-2000
International Osteoporosis Foundation/European Society for Economic Aspects of Osteoporosis and Osteoarthritis	2013	≥ 1000	800
United States Preventive Services Task Force§	2013	—	—
National Osteoporosis Foundation	2014		
Men 50–70		1000	
Men >70 and women >50		1200	800-1000
American Geriatrics Society (for community dwelling adults >65 years)	2014	1000-1200	>1000

* References given in appendix A on thebmj.com.

† Sponsored by the European Foundation for Osteoporosis and Bone Disease, the National Osteoporosis Foundation, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases

‡ Parent organisation for International Osteoporosis Foundation.

§ Calcium and vitamin D not recommended for primary prevention of fracture.

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Table 2| Harms reported from randomised trials of calcium supplements, vitamin D supplements, or their combination

Type of study, year*	Intervention	Adverse outcome	Risk estimate (95% CI)
RCT, 2005	Calcium	Gastrointestinal symptoms	1.37 (1.20 to 1.57)
RCT, 2006	Calcium	Constipation	1.63 (1.26 to 2.10)
RCT , 2006	Calcium	Constipation	1.48 (1.11 to 2.00)
RCT , 2006	Calcium + vitamin D	Kidney stones	1.17 (1.02 to 1.34)
RCT , 2007	Vitamin D	Hip fracture	1.49 (1.02 to 2.18)
RCT, 2010	Vitamin D	Total fractures	1.26 (1.00 to 1.59)
		Falls	1.15 (1.02 to 1.30)
Meta-analysis of RCTs, 2010	Calcium	Myocardial infarction	1.27 (1.01 to 1.59)
Meta-analysis of RCTs , 2010	Calcium	Cardiovascular events	1.14 (0.92 to 1.41)
Meta-analysis of RCTs, 2011	Calcium ± vitamin D	Myocardial infarction	1.24 (1.07 to 1.45)
		Stroke	1.15 (1.00 to 1.32)
Meta-analysis of RCTs, 2012	Calcium	Gastrointestinal symptoms	1.43 (1.28 to 1.59)
RCT, 2012	Calcium	Hospital admission for gastrointestinal symptoms	1.92 (1.21 to 3.05)

RCT= randomised controlled trial.

*References are in the appendix A on thebmj.com.

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Table 3 | Sponsorship of osteoporosis advocacy organisations and specialist societies by the nutrition industry

Organisation	Industry sponsor		
	Drug or diagnostics	Food manufacturer	Other
National Osteoporosis Foundation	Bayer Healthcare, Lane Laboratories, Mission Pharmacal, Novartis, Pharmavite, Pfizer, Roche, Warner Chilcott, Eli Lilly		Council for Responsible Nutrition, Health Monitor Network, FoodCare
International Osteoporosis Foundation	Amway, GlaxoSmithKline, Takeda, Pfizer, Teva, DSM, Immunodiagnostic Systems, Warner Chilcott, Eli Lilly, Merck	Fonterra, Nestle, Mengniu Dairy Company, Danone	
American Society for Bone and Mineral Research	Pfizer, Eli Lilly		
International Bone and Mineral Society	Warner Chilcott, Roche, Eli Lilly, Sanofi		
European Calcified Tissue Society	Eli Lilly		
European Society for Economic Aspects of Osteoporosis and Osteoarthritis	Eli Lilly, Merck, RottaPharm Madaus		
Vitamin D Council	Bio-tech Pharmacal, WLS Products, ZRT Laboratory		Sperti/KBD

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Figure

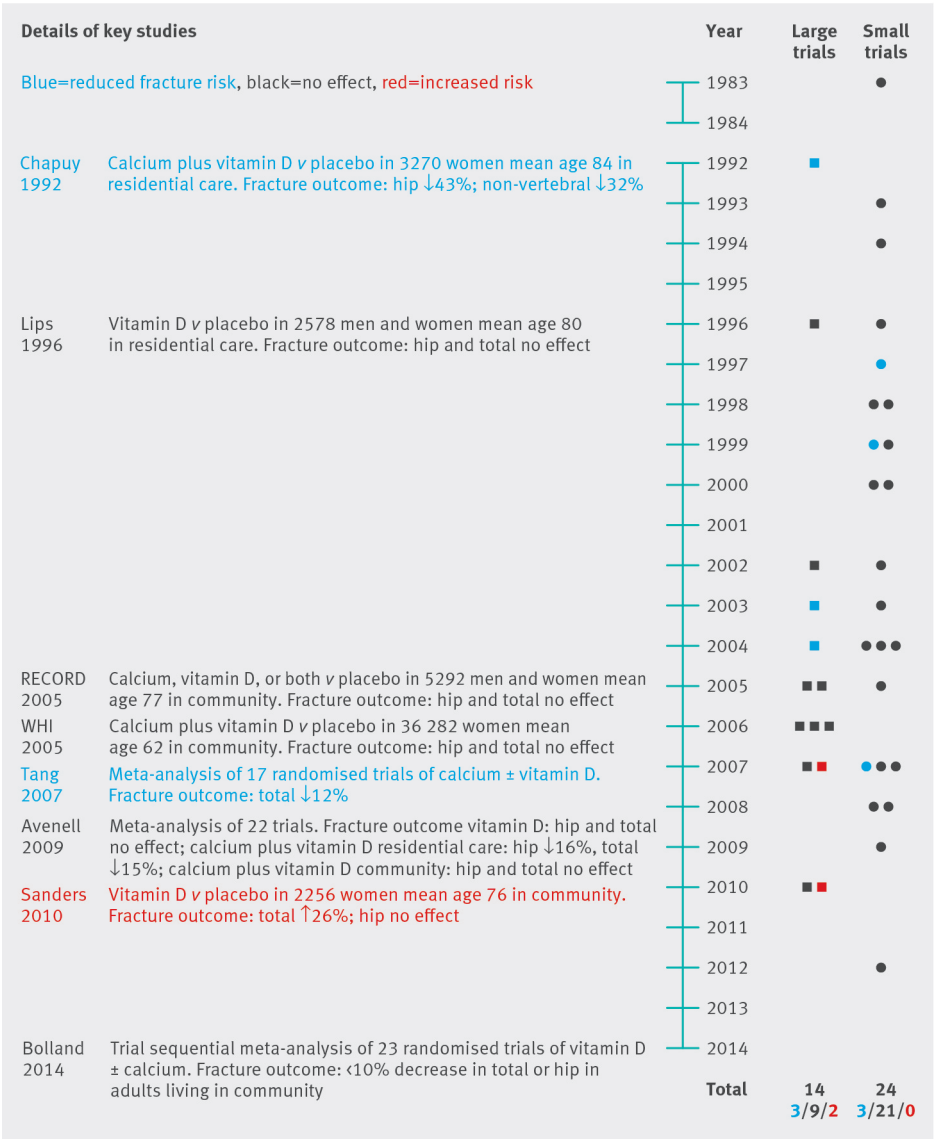

Fig 1 Timeline of evidence from randomised trials of calcium with or without vitamin D with fracture as an outcome. Trials were identified by systematic database searches. Key studies are as indicated, with brief summaries of trial characteristics. Large trials had >1000 participants. References are in appendix A on thebmj.com

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