In the Women’s Health Initiative (WHI) calcium plus vitamin D trial, a large cohort (more than 36,000) of postmenopausal women between the ages of 50 and 79 years received 500 mg of calcium carbonate with 200 IU of vitamin D3 twice daily, or matching placebos, for an average follow up of 7 years (1). The primary outcome variable was hip and other fractures. In the intention-to-treat analysis, there were no significant effects of calcium with vitamin D supplementation on total, hip and other site-specific fracture rates. However, in a subgroup analysis among the 60% of women who were adherent to supplementation (defined as those who took at least 80% of their study medication), the risk of hip fractures was reduced by 29% (hazard ratio, 0.71; 95% confidence interval, 0.52-0.97). Furthermore, in the subgroup of women aged 60 years and older, the risk of hip fractures was reduced by 21% (hazard ratio, 0.79; 95% confidence interval, 0.64-0.98).

There are a number of factors that may have contributed to the null finding in the primary intention-to-treat analysis. This was a community based trial among healthy postmenopausal women with a wide age range, and the subjects were not selected on the basis of low bone mineral density, low calcium intake or vitamin D status, or other risk factors for osteoporosis. In addition, two thirds of the subjects had an adequate baseline daily calcium intake from diet and supplements (approximate mean calcium intake 1150 mg/day) and 40% had a daily vitamin D intake of at least 400 IU. As noted by the study authors, the dose of vitamin D used may not have been sufficient, since previous trials have reported beneficial effects on fracture risk reduction at doses of 600 IU or higher. Furthermore, the study design allowed for the use of bone-trophic agents such as bisphosphonates, calcitonin and hormone replacement therapy. More than half of all participants in the intervention and placebo groups were receiving hormone-replacement therapy for the duration of follow up, which may have contributed to the lower than anticipated rate of hip fractures in the placebo group and hence reduced power of the study (from 85% to 48%, for detecting an 18% reduction in hip fractures in the intervention group). An additional observation in this study was a 17% increased risk of kidney stones among the supplemented participants. Despite the overall null finding in this community based trial, the benefits of calcium and vitamin D supplementation for reducing non-vertebral fracture rates in at-risk populations, such as men and women over 65 years and the institutionalised elderly, have been demonstrated in other trials. The WHI trial also highlights the need for ensuring patient compliance with supplementation. An editorial accompanying the WHI publication supports the recommendation that women consume the recommended daily levels of calcium and vitamin D through diet, supplements or both (2). In patients diagnosed with osteoporosis, additional therapeutic agents may be indicated, and in this case calcium and vitamin D supplements are usually also prescribed as co-therapy.