

Appendix C

Summary of Intervention Studies

Literature Citation	Study Design	Number and Description of Subjects	Duration of Study	Specifics of Intervention Including Source and Identity of Test Material	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Dawson-Hughes, B <i>et al.</i> . Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. <i>Ann Int. Med.</i> 1991;115:505.	Double-blind, placebo-controlled, randomized intervention. Measured: Spine and whole-body BMD by DXA; serum PTH and 25-(OH)D	N=249 white, healthy, postmenopausal women. Subjects had participated in a previous calcium-supplementation trial at the center. Exclusion criteria included use of estrogen or other medicines known to affect calcium or bone metabolism; 2 SD or more below age-matched BMD.	12 months	Treatment group (n=124) received 400 IU vitamin D/d (form not specified) Placebo group (n=125) Subjects stratified according to baseline calcium intake prior to randomization. All subjects received 377 mg calcium (127 from Ca phosphate, 250 mg from calcium citrate malate.	Habitual diet. Ca and vit D intakes of basal diet were estimated using a FFQ		27 subjects out of 276 failed to complete the study (n=15 vit D; 12 placebo). Physical activity was similar in both groups	The placebo group had no net change in BMD (although BMD increased in period 1 (~the first 6 months) and decreased in period 2 (~the second 6 months) for no net change. The vitamin D group had similar increases in spinal BMD as the placebo group in period 1 but less decrease in period 2. Net result was an increase in spine BMD of 0.85% (p=0.04). In period 2, 25-OH-D levels were lower and PTH levels higher in the placebo group.	The authors conclude that postmenopausal women with vitamin D intakes of 100 IU can reduce late wintertime bone loss and improve net bone density of the spine over the year by increasing intake to 500 IU daily.

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<p>Chaput, MC <i>et al.</i>. Vitamin D3 and calcium to prevent hip fractures in elderly women. New Eng. J. Med. 1992;327:1637</p>	<p>Randomized, placebo-controlled intervention</p> <p>Measured: hip and other nonvertebral fractures; BMD at four sites by DXA; serum PTH, 25-(OH)D and several other serum biomarkers</p>	<p>N=3,270 healthy ambulatory women, mean age=84 years. Exclusion criteria included use of drugs known to alter bone metabolism within the past year. Vitamin D or calcium treatment during the past year. Estrogen use was not excluded, but <1% of subjects had received HRT after menopause.</p>	<p>18 months</p>	<p><u>Experimental group:</u> N=1,634 received 800 IU vitamin D3 and 1200 mg calcium as tricalcium phosphate per day.</p> <p><u>Placebo group:</u> N=1,634 Two pills per day containing lactose and a suspension of lactose, kaolin and starch.</p>	<p>Habitual diet</p>		<p>46% of both experimental and control groups failed to complete the study. The two top reasons were death and failing to consume at least 70% of the pills. There were no differences in non-compliance between the two groups</p>	<p>The experimental group who had been followed for 18 months had 43% fewer hip fractures ($p=0.43$) and 32% fewer nonvertebral fractures ($p=0.15$) than controls.</p> <p>The experimental group experienced a 44% reduction in serum PTH ($p<0.001$) and a 162% increase in 25-(OH)D compared to baseline.</p> <p>BMD of the proximal femur increased 2.7% in the experimental group and decreased 4.6% in the placebo group ($p<0.001$)</p>	<p>The authors concluded that supplementation with vitamin D and calcium reduces the risk of hip fractures and other nonvertebral fractures among elderly women.</p>

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Johnston, C.C. <i>et al.</i> Calcium supplementation and increases in bone mineral density in children. <i>New Eng. J. Med.</i> 1992;327:82.	Randomized, placebo-controlled intervention Measured: Radial bone mass with Lunar SP-2 absorptiometer; Forearm length	N=45 pairs (86 female, 54 male) of healthy, white, identical twins, age=6-14 years. Exclusion criterion was Ca intake >1,200 mg/d 22 pairs were pre-pubertal throughout the study, 4 pairs were post-pubertal at baseline and 19 pairs underwent puberty during the study	3 years	<u>Treatment:</u> One twin in each pair was randomly assigned to receive 1000 mg/d calcium citrate malate provided in 4 250 mg capsules (two in the morning and two at night). <u>Control:</u> The other twin in each pair received an identical-looking placebo.	Habitual diet. One day food records were collected during monthly home visits. Baseline calcium intake was 839 mg/d in the treatment group and 889 mg/d in the placebo group.		25 sets of twins failed to complete the study. More boys than girls dropped out, usually because they no longer wanted to take the pills. There was no difference in baseline bone density between the subjects who dropped out and those who completed the study. Physical activity was monitored throughout the experiment by questionnaire. The children did not smoke or use alcohol.	Calcium supplementation resulted in greater increase in BMD (1.4% average over six sites). However, the effect was much greater (2.9%) in prepubertal subjects compared to those who had already been pubertal at baseline or experienced puberty during the study (0.3%). There were no significant differences in physical activity.	Calcium supplementation increased BMD in prepubertal children who were consuming approximately the recommended amount of dietary calcium. Calcium supplementation did not have a significant effect after sexual maturation, however the effects of puberty, the difficulty of measuring BMD in rapidly growing children or statistical power of the study may have been limiting factors in detecting small, but important, changes in BMD in adolescent children.

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<p>Lloyd, T. <i>et al.</i> Calcium supplementation and bone mineral density in adolescent girls. <i>J. Am. Med. Assn.</i> 1993;270:841.</p>	<p>Randomized, double-blind, placebo-controlled intervention.</p> <p>Measured: BMD and bone mineral content of lumbar spine and total body calcium by DXA; 24-hr urinary Ca excretion.</p>	<p>N=94 white, healthy females; mean age=11.9 yr. Subjects were premenarchal, between 80 and 120% of ideal body weight and were not taking medication regularly.</p>	<p>18 months</p>	<p><u>Treatment:</u> 250 mg calcium citrate malate</p> <p><u>Control:</u> Identical-looking pill containing micro-crystalline cellulose.</p> <p>A stratified randomization procedure was used to assure equal distribution of BMI and initial bone density between the two groups.</p>	<p>Habitual diet.</p> <p>Dietary Ca at baseline was ~960 mg/d for both groups</p>		<p>18 participants dropped out of the study. There were no differences at baseline in age, height, weight, BMI or LSBMD between subjects who completed the study and those who did not.</p>	<p>Compared to the placebo group, the experimental group had greater increases of lumbar spine BD (3.4%, $p=0.03$); lumbar bone mineral content (4.7%, $p=0.06$) and total body BMD (1.3%, $p=0.05$).</p> <p>Dietary calcium intake during the study was 935 mg/d in the control group and 1,370 mg/d in the treatment group ($p=0.14$).</p>	<p>The authors conclude increasing daily Ca intake from 80% of the recommended daily allowance to 110% via supplementation resulted in an increment of 24g of bone gain per year.</p>

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Reid, I. <i>et al.</i> Effect of calcium supplementation on bone loss in postmenopausal women. N. Engl. J. Med. 1993; 328:7	Randomized, double-blind, placebo-controlled intervention. Measured BMD of whole body (including arms, legs and trunk), lumbar spine (L2 to L4) and proximal femur. Fasting blood samples of serum ionized calcium, creatinine, PTH (intact), 25-hydroxy-vitamin D, and Alkaline Phosphatase. Second urination fasting urine samples of hydroxyproline and creatinine. 24-hour urine samples for calcium and creatinine (baseline, 3mo, 2yrs).	135 Post-menopausal Female Subjects (menopause +3 years prior) with a mean dietary calcium intake of 750mg/day. <u>Exclusion criteria:</u> include the following: calcium metabolism history including symptomatic vertebral fractures; renal, thyroid, or hepatic dysfunction; current symptomatic disease; HRT usage within 3 years; supra-physiologic glucocorticoid dosages for more than 6 months at a time, or concurrent use of glucocorticoids, anticonvulsants, or thiazide diuretics	2 years	<u>Treatment:</u> N=61, 1000mg elemental calcium delivered in a 5.24g calcium lactate-gluconate and 0.8g calcium carbonate effervescent tablet. <u>Control:</u> N=61, Identical effervescent sucrose placebo tablet. Both tablets from Sandoz	<u>Treatment:</u> Twice-daily self-administration of calcium (84±7 % compliance) or placebo tablet (83±10 % compliance). <u>Control:</u> Habitual diet. Baseline dietary calcium was 760±300 mg/day for treatment group and 730±290 mg/day for the placebo group.		13 participants dropped out: 3 left the country, 3 began physician administered HRT, 1 personal reasons, 6 intercurrent illnesses. 4 of 6 illnesses were found not related to study. 1 participant developed renal calculus. An other participant developed an exacerbation of a preexisting dyspeptic symptom. No significant difference between the characteristics of either group after participant withdrawal. Fractures and areas of previous residual contrast medium removed from BMD measures.	Whole-body BMD declined in both groups (P<0.001), but a significantly greater decline was observed in the placebo group (P<0.005). Lumbar spine BMD increased with calcium supplementation (P<0.001). No net change detected in placebo group. The lumbar BMD between the two groups was statistically different (P=0.04). In the femur, BMD declined less with calcium supplementation; however, significance was only found in Ward's triangle (P=0.04). Total body bone loss rates were only examined during the 2 nd year of the study. The rate of bone loss was greater in the placebo group (P=0.05). Only urinary hydroxyproline and calcium excretion were significantly different	

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Aloia JF <i>et al.</i> Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. <i>Ann Internal Med.</i> 1994;120:2	Three-arm, placebo-controlled, randomized parallel trial. Main outcome measures: total body calcium by delayed gamma neutron activation analysis and whole body counting; BMD of the spine (L2 – L4), femur, and radius by photon absorptiometry; routine biochemical laboratory studies.	(N=118) Healthy, white women 3 – 6 years post spontaneous menopause. Exclusion criteria: any disorder or medication known to affect bone metabolism including glucocorticoid use, gastrointestinal disease; previous or current malignancy; absolute contraindications to estrogen replacement therapy including estrogen-dependent neoplasm of the breast or uterus, undiagnosed vaginal bleeding, thrombophlebitis, thromboembolism, acute liver disease; or other chronic diseases.	2.9±1.1 years	<u>Experimental groups:</u> Group 1: hormonal replacement (estrogen – progesterone – calcium carbonate) in the form of 0.625 mg/day (days 1 – 25) conjugated equine estrogens (Premarin, Wyeth-Ayerst Laboratories, Inc.) along with 10 mg/day (days 16 – 25) medroxyprogesterone (Provera, Upjohn). Group 2: Calcium carbonate (Caltrate, Lederle) **All women in both treatment groups received 400 IU vitamin D by multivitamin**	Habitual diet. Daily calcium intake range: 150 – 1263 mg		Subjects with known osteoporosis or a vertebral fracture were not eligible for the study. 17 subjects withdrew from the study for various reasons. One subject developed breast cancer. This subject was not a member of the HRT group. The authors did not state if this withdrawal resulted in differences between overall participant characteristics. Years post menopause was related to total body calcium, BMD (femoral neck, Ward triangle) by ANCOVA. The means were adjusted for this effect.	Rates of change in bone mineral were statistically significantly different ($P<0.01$) as compared to baseline in the sites: Total body, spine, femoral neck, Ward triangle, and the trochanter, but not in the radius. Similar to the placebo group, statistically significant changes in bone mineral of the calcium supplemented group (group 2) were observed at the following sites: Total body ($P<0.01$), spine ($P<0.01$), femoral neck ($P<0.05$), Ward triangle ($P<0.01$), and trochanter ($P<0.01$), but not at the radius. A fewer number of sites were significantly different in the HRT group (group 1). Only in the total body calcium and the trochanter were significant rates of change observed ($P<0.01$).	The authors conclude that although less effective than estrogen-progesterone-calcium augmentation alone significantly retards bone loss from the femoral neck and improves calcium balance in recently postmenopausal women. The authors further conclude that dietary calcium augmentation should be recommended as a strategic option in helping to prevent postmenopausal bone loss.

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				<p><u>Control group:</u> placebo</p> <p><u>Protocol:</u> All subjects: Women were stratified for years postmenopause</p>					

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Chapuy, M C et. al.. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ, 1994; 308:1081.	<p>Dietary intervention</p> <p>Measured: hip fractures; all non-vertebral fractures</p>	N=3270 mobile elderly women with a mean age of 84 (SD 6) years living in 180 nursing homes	3 years	<p>1) Received 1.2 g calcium daily in the form of tricalcium phosphate + 800 IU (20µg) cholecalciferol n=1635</p> <p>2) Received a double placebo n=1635</p>	Information not given			<p>The active treatment analysis shows that after 36 months of follow up the probability of hip fractures (-29%; P<0.01) and all non-vertebral fractures (-24%; P<0.01) were reduced in the treatment group. The intention to treat analysis shows that 17.2% fewer subjects had one or more non-vertebral fractures (255 v 308, P<0.02) and 23.0% fewer subjects one hip fracture (137 v 178, P<0.02) in the treatment group. In addition there was a decreased probability of hip fractures (P<0.02) and all non-vertebral fractures (P<0.01). Women with a raised mean serum PTH concentration and low serum 25-hydroxycholecalciferol concentration at baseline had normal values after 3 years of treatment. In the placebo group, PTH significantly increased from baseline values, and 25-hydroxycholecalciferol concentration remained low. Femoral bone density was measured at baseline in 128 women and a significant negative correlation was found between density and serum PTH concentrations before (r=0.34) and after adjustment for age (r=0.25).</p>	<p>The authors conclude that there is a preventive effect of calcium and cholecalciferol supplementation on the risk of hip fracture. Daily supplementation with cholecalciferol and calcium salts is the most certain and safest way to reduce the risk of hip fracture because of the side effects of physiological doses are negligible.</p>

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Chevalley, et. al. Effects of Calcium Supplements on Femoral Bone Mineral Density and Vertebral Fracture Rate in Vitamin-D-Replete Elderly Patients. Osteoporosis Int. 1994: 4:245	Randomized placebo-controlled double-masked study Measured: Femoral shaft (FS), Femoral neck (FN), and Lumbar spine (LS) bone mineral density (BMD)	N=93 healthy subjects (72.1 ± 0.6 years), ambulatory, 82 women, 11 men, recruited from osteoporosis meeting and retirement homes N=63 suffered a recent hip fracture, 55 women, 8 men, (78.4 ± 1.0 years) Exclusion criteria: parathyroid, thyroid, hepatic or cardiac disorders, Paget's disease of bone, plasma creatinine above 160 µmol/l, or who had received treatment with corticosteroids, estrogens, anticonvulsants, calcitonin, or fluoride during the year prior to study, or supplements of Ca or Vitamin D during previous 2 months, hip fracture from severe trauma, metastases or non-metabolic bone diseases, significant mental impairment were excluded	18 months	Subjects without hip fractures: 1. Placebo (n=31) 2. Osseino-mineral complex (n=31) 800 mg elemental calcium/d 3. Calcium carbonate (n=31) Subjects with recent hip fractures: Randomized into 2 groups (same treatments as number 2 and 3 above. No placebo group for ethical reasons.	Habitual	All subjects received a single oral dose of 300,000 IU vitamin D ₃ at the beginning of the study and were instructed to take 4 tablets of Ca daily in 2 doses at meal times.	13 of the 93 non-fractured subjects and 20 of the 63 fractured subjects dropped out because of gastrointestinal discomfort (constipation, abdominal distension or nausea), loss of interest, death, cancer, thyroiditis, polymyalgia rheumatica, primary hyperparathyroidism, prolonged immobilization or contra lateral hip fracture.	FS BMD changes in Ca-supplemented non-fractured women were significantly different from those in the placebo group (+0.6 ± 0.5% v -1.2 ± 0.7%, p<0.05). There was no difference in effect between the 2 forms of Ca. The changes of +0.7 ± 0.8% v -1.7 ± 1.6% in FN BMD of Ca-supplemented women and the placebo group did not reach statistical significance. In fractured patients, FS, FN, and FS BMD changes were -1.3 ± 0.8, +0.3 ± 1.6 and +3.1 ± 1.2% (p<0.05 for the last). The rate of new vertebral fractures was 74.3 and 106.2 fractures per 1000 patient-years in Ca-supplemented non-fractured subjects and in the placebo group, respectively, and 144.0 in Ca-supplemented fractured patients. No significant difference in Ca consumption from dairy products between fractured and non fractured subjects.	The authors concluded that oral Ca supplements prevented a femoral BMD decrease and lowered vertebral fracture rate in the elderly.

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<p>Elders PJM <i>et al.</i> Long-term effects of calcium supplementation on bone loss in perimenopausal women. <i>J. Bone Miner. Res.</i> 1994; 9:7</p>	<p>Randomized, controlled double-blind longitudinal trial.</p> <p>Measured: BMD of lumbar spine (L2 – L4) by dual-photon absorption; combined metacarpal cortical thickness by radiographs of both hands; serum intact PTH; serum 25-hydroxy vitamin D and 1,25-hydroxy vitamin D; serum osteocalcin; and other serum and urinary biochemical markers</p>	<p>N=295 Dutch women aged 46 to 55 years.</p> <p>Exclusion criteria: medical history of hysterectomy, oophorectomy, use of hormonal contraceptives, postmenopausal estrogen supplementation, renal failure, metabolic bone disease, and urolithiasis.</p> <p>Subjects were stratified according to menopausal status.</p>	<p>24 months (with an additional 12 month study continuation)</p>	<p><u>Experimental groups:</u></p> <p>Group 1: N=66 received 1000mg Ca²⁺ effervescent tablet once daily at bedtime.</p> <p>Group 2: N=64 received 2000mg Ca²⁺ in the form of 1000mg effervescent tablet twice daily in morning and evening.</p> <p>Experimental treatment was administered in the form of an effervescent tablet containing 5.23g calcium lactogluconate and 0.9g calcium carbonate (Sandoz). Each tablet contained 1000mg Ca²⁺.</p> <p><u>Control group:</u> N=84 did not receive calcium</p>	<p>Habitual diet</p>		<p>35 subjects were switched to a calcium citrate supplement (4.18g calcium citrate) after gastrointestinal complaints.</p> <p>47 participants withdrew from the initial 2 year clinical trial for reasons not stated. The investigators did not state if these dropouts resulted in a significant difference in the characteristics between those who dropped out and those who remained in the study.</p> <p>Six subjects later classified as premenopausal, were included in the perimenopausal group.</p>	<p>Significant bone loss occurred in the control group (p<0.01) of pre- and early perimenopausal subjects, but not in the experimental groups.</p> <p>Significant bone loss was observed in the perimenopausal and postmenopausal subjects of both the control and experimental treatment groups (p<0.001).</p> <p>Rate of bone loss was significantly less in the experimental groups as compared to the control group (p<0.01) during the first year.</p> <p>Changes in MCT were not significantly different between any menopausal group. However, bone loss was significantly lower in the experimental group (p<0.01).</p> <p>Serum 1,25-dihydroxy vitamin D significantly decreased in both treatment groups (p<0.001).</p>	<p>The authors conclude that calcium supplementation substantially reduces cortical and trabecular bone loss in the years immediately preceding menopause. In addition, it reduces postmenopausal cortical bone loss to some extent, it does not prevent menopause-related lumbar bone loss.</p>

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				supplementation. The authors did not report if a placebo was used in this trial.					

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Reid, I et. al.. Determinants of the rate of bone loss in normal postmenopausal women. Journal of Clinical Endocrinology and Metabolism, 1994; 79:950	Prospective randomized placebo-controlled trial Measured: BMD	N=122 normal postmenopausal white women with an avg. age of 58.1 ± 5.0 yr None used drugs or had diseases influencing Ca metabolism.	2 years	Calcium group: 1g/day Placebo group: No further information was provided	Average Ca intake of 762 ± 287 mg/day		N=122 completed the study	Univariate correlation coefficients indicated that Δ BMD at most sites was inversely related to baseline BMD and positively related to rate of change in body weight ($0.10 < r < 0.36$) and fat mass ($0.11 < r < 0.42$) during the study. Lean mass and its rate of change showed no consistent relationship to Δ BMD. There was no correlation between Δ BMD and any of the lifestyle, muscle strength, dietary, or hormonal indices or with severity of spinal osteoporosis. Multiple regression analysis indicated that Δ BMD in the total body was directly related to fat mass ($P < 0.0001$), the rate of change in fat mass ($P < 0.0001$), the renal tubular reabsorption of Ca ($P < 0.01$), and Ca treatment ($P < 0.01$) and inversely to the initial BMD ($P < 0.0001$; $r^2 = 0.42$; $P < 0.0001$). Similar effects were seen throughout the study.	The authors conclude that baseline bone density, fat mass, and renal calcium handling are important factors influencing bone loss in normal postmenopausal women.

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Strause L <i>et al.</i> Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. J. Nutr. 1994;124:1060	Randomized double-blind, placebo-controlled trial Measured: BMD of the lumbar (L2 – L4) spine by DEXA and dietary calcium intake by food frequency questionnaire	Women (N=113) aged 50 years or older (average age = 66±7 years) in general good health as measured by medical history and routine clinical blood analyses. Exclusion criteria: positive Pap smear or mammogram during the previous year; any disease or condition known to affect bone or calcium metabolism; history of chronic renal, hepatic, or gastrointestinal disease; evidence of collapsed or focal vertebral sclerosis.	24 months	<u>Experimental groups:</u> Group 1) placebo calcium, active trace minerals Group 2) active calcium, placebo trace minerals Group 3) active calcium, active trace minerals <u>Control group:</u> Placebo calcium and placebo trace minerals <u>Treatments:</u> subjects received placebo or 1000 mg elemental calcium (calcium citrate malate) per day. Two 250 mg tablets with morning meal and two tablets 2 hours after evening meal. Trace minerals were 15mg Zinc, 2.5mg Copper, and 5mg Manganese gluconate salts.	Habitual diet.		54 participants did not complete the study. 21 subjects withdrew due to adverse symptoms believed related to the supplements. 16 subjects withdrew for personal reasons. Eight subjects were dropped because they began estrogen replacement therapy. The authors did not state if this participant withdrawal changed the overall characteristics of the participants. Dietary trace mineral intake, vitamin D intake, and physical activity were not measured.	Dietary calcium intakes between initial and final measurements were not significantly different (582 vs. 638 mg/day, respectively). By two-way ANOVA analysis, there was no significant interaction between calcium and trace mineral supplements. The overall ANOVA for percent change in spinal bone density was significant (P=0.033), as was the main effect for calcium supplementation (P=0.045). The main effect for trace minerals was not significant (P=0.12). Loss of bone density was the greatest in the placebo group and was statistically different as compared to the baseline measurement (P = 0.0061). Calcium plus trace minerals was the only treatment significantly different from placebo (P = 0.0099).	The authors state that these data suggest that bone loss in calcium supplemented, older postmenopausal women can be further arrested by concomitant increases in trace mineral intake.

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Chan, G <i>et al.</i> Effects of dairy products on bone and body composition in pubertal girls. J. Ped. 1995; 126:4	Randomized controlled study. <u>Measured:</u> BMC and density by single photon and dual energy x-ray absorption (DEXA) of the radius, femoral neck, lumbar spine, and total body at initiation, 3, 6, 9, and 12 months there after. Body composition (lean body mass and body fat) by DEXA. Serum calcium, phosphate, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, alkaline phosphatase, magnesium, albumin, urinary calcium/creatinine ratio, and hydroxyproline	48 white girls (mean age = 11 years and sexual development at Tanner Stage 2) <u>Exclusion criteria:</u> Participation in sport activities; chronic diseases that would affect growth or calcium metabolism; participant height and weight must not be lower than the 10 th percentile or higher than the 90 th percentile.	1 year	Weekly, girls in the dairy group selected dairy products from a list of varying calcium and fat content under the supervision of a clinical research center dietary staff to meet the minimum 1200mg calcium daily requirement. Food products were delivered weekly and all unused products were removed and counted. 3-day dietary history and food frequency collected at study initiation, 3, 6, 9, and 12 months post initiation.	<u>Treatment:</u> Habitual diet supplemented with dairy products containing at least 1200mg calcium daily. <u>Control:</u> Habitual Diet	1 year	2 participants withdrew; those results were excluded from the study. This study provided calcium and vitamin D in the form of dairy products so it is not possible to conclude that the positive effects were due to calcium and vitamin D <i>per se</i> , however, it does provide evidence that these two nutrients promote optimal bone health. The lack of a placebo group (i.e. dairy products without calcium or vitamin D) also complicate interpretation of this study, but nutrient intake of most nutrients was similar between the two groups.	<u>Treatment group:</u> significantly greater increases in BMD of the lumbar spine and total body bone mineral. Lumbar density increases associated with average dietary calcium and vitamin D intake ($r = 0.37$ for calcium, $r = 0.41$ for vitamin D; $p < 0.01$). No difference in bone mineral content, lean body mass, or body fat percentage between groups. No difference in weight or height gain between groups. No differences in serum or urinary biochemical assays.	

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Fujita T <i>et al.</i> Effect of calcium supplementation on bone density and parathyroid function in elderly subjects. Miner. Electrolyte Metab. 1995;21:229	Randomized, double-blind, placebo-controlled trial. Measured: Lumbar spine BMD (L2 – L4) and midradial BMD by DEXA; Total body calcium content by DEXA; urinary calcium/creatinine ratio; serum alkaline phosphatase and intact PTH.	58 hospitalized patents aged 65 to 95 years. Exclusion criteria: participants with a compression fracture or marked osteophyte formation in L2 – L4 were excluded.	24 months	<u>Experimental groups:</u> Group 1: 150 mg heated oyster shell-seaweed calcium (HOSS Ca) in the form of 6 tablets given 3 times daily. Group 2: 150 mg Calcium Carbonate in the form of 6 tablets given 3 times daily. ** Both supplements provide a total of 900 mg calcium supplementation ** <u>Control group:</u> Placebo tablets given as 6 tablets 3 times daily. <u>Protocol:</u> random assignment to groups of similar age and lumbar spinal bone density.	Regular hospital diet. Dietary calcium intake was approximately 600 mg/day.		Although the authors mention that measurements were taken through the 24 th month, results from month 24 were not found in the discussion or in the results section of this paper. The authors state in the introduction that the results listed were preliminary.	The lumbar spine BMD was significantly higher (P=0.014) in treatment group 1 as compared to placebo at 18 months. This trend was also observed at 6 months (P=0.015), and 12 months (P=0.008). Similarly, treatment group 1 was significantly higher (P=0.02) than treatment group 2 at 6 months. However, the values in treatment group 2 were not significantly different than those in the placebo group. The midradial BMD was significantly higher (P<0.05) from baseline to 18 months in treatment group 1 as compared to placebo. Total body calcium content ratio between the 12 th and 18 th months was significantly higher in treatment group 1 than either treatment group 2 or placebo (P=0.0292 and 0.0321, respectively). The biochemical markers, Ca/Cr ratio and alkaline phosphatase tended to be higher in the placebo group except for serum intact PTH which decreased in treatment group 1.	The authors conclude that these findings suggest the most effective suppression of parathyroid function and bone resorptive changes was by oyster shell-seaweed calcium followed by calcium carbonate. They continue to state that HOSS Ca appears to be useful to supplement calcium deficiency and secondary hyperthyroidism in elderly subjects.

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Haines CJ <i>et al.</i> Calcium supplementation and bone mineral density in postmenopausal women using estrogen replacement therapy. Bone 1995; 16:5	Randomized controlled study. Measured BMD in lumbar spine (L2 – L4), femur neck, trochanter, and Ward's triangle by bone densitometry.	102 postmenopausal women <u>Selection criteria:</u> total abdominal hysterectomy; bilateral salpingo-oophorectomy; absence of recognized contraindications to HRT	12 months	<u>Control:</u> (N = 53) Conjugated Estrogen (0.625 mg/day; Premarin, Wyeth-Aysert International) <u>Treatment:</u> (N = 49) Conjugated estrogens (0.625 mg/day) + 1000mg elemental calcium (Calcium Sandoz, Sandoz Pharma LTD)	<u>Control:</u> Habitual diet + daily HRT medication <u>Treatment:</u> Habitual diet + daily HRT medication + 1000mg calcium supplement. Baseline calcium intake median based on questionnaire. <u>Control:</u> 319.0±214.1 mg/day <u>Treatment:</u> 363.5±204 mg/day (median±IQR)		7 subjects withdrew from treatment group due to gastrointestinal discomfort; results excluded from study	<u>Treatment group:</u> Significant increase in the femoral neck, but not in the other areas of the femur nor of the lumbar spine.	The authors suggest that the results of this study indicated the addition of supplemental calcium may improve bone mass of post menopausal women using estrogen replacement therapy who have a low dietary calcium intake. The authors also state that the duration of this study was not sufficient to make conclusions about the enduring effect of treatment.

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Lee WTK <i>et al.</i> A randomized double-blind controlled calcium supplementation trial, and bone and height acquisition in children. <i>Brit. J. Nutr.</i> 1995; 75:125	Randomized double-blind placebo controlled trial Measured: bone mineral acquisition, BMC and BMD in the distal radius, lumbar spine (L2 - L4), and proximal femur; height increment.	109 healthy Hong Kong Chinese children (63 boys and 46 girls) aged 7 years. These study children came from a longitudinal growth study (Leung and Lui, 1989; Lee <i>et al.</i> 1993). No recent metabolic disorder or incident of fractures which might directly or indirectly affect bone metabolism were present in these children.	18 months	<u>Experimental group:</u> (N=54, 32 boys and 22 girls) received 300 mg Calcium Carbonate in the form of cherry-flavored chewable tablet (Tums-Ex; Smithkline Beecham) <u>Control group:</u> (N=55, 31 boys and 24 girls) received sucrose placebo tablets produced by the same manufacturer as the calcium supplement.	Habitual diet		87 of the original 109 completed the study (3/87 moved away before the last measurement). The authors state that there was no significant difference between the overall characteristics of the two group's dietary intake. However, in the experimental group, height increment was slightly higher (P=0.036) among drop-outs (N=11) than their successful counterparts, whereas radial BMC:BW was lower (P=0.033) in the drop-outs. Additionally, Lumbar spine BMD was significantly lower in the drop-outs (N=14) than in the successful participants (N=40) with 2.8±2.9 vs. 5.6±3.9 (P=0.027).	The experimental group had significantly greater gains in lumbar spine BMC (P=0.035) and lumbar spine area (P=0.049) than the control group. Lumbar spine BMD was not significantly different between the two groups. A greater increase in radial BMC:BW (P=0.081) as compared to control group was observed. No significant difference in weight, height, amount of physical activity, or 25-hydroxyvitamin D levels between the two groups. Only treatment effect (r=0.32, P=0.0041) and baseline Ca intake (r=0.29, P=0.0089) were significant indicators of the net increase in lumbar spine BMC. Increased radial BMD (P=0.081) in the experimental group.	The authors suggest that these results confirm a positive effect of calcium on bone mass of the spine and the radius, but no effects on the femoral neck or height increase. The authors further state that a longer trial is warranted to confirm a positive calcium effect during childhood that may modify future peak bone mass.

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Ooms ME <i>et al.</i> Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trail. J. Clin. Endo. Metabol. 1995; 80:4	Randomized double-blind trail Measured BMD in both hips (femoral neck and trochanter) and distal radius by DEXA. Measured biochemical markers of bone turnover	348 women aged ≥ 70 years Exclusion criteria: history of hip fracture, total hip prosthesis, history of urolithiasis, hypercalcemia, or sarcoidosis.	2 years	<u>Control:</u> (N=171) placebo of similar design to treatment <u>Treatment:</u> (N=177) 400 IU Vitamin D ₃ tablet	<u>Control:</u> habitual diet + placebo tablet once daily <u>Treatment:</u> habitual diet + 400 IU Vitamin D ₃ tablet Calcium intake was estimated to be 200-300 mg/d by a FFQ related to dairy products. This calcium intake is probably an underestimate of actual intakes.		Small group of subjects (N=13) taking pills supplemented with Vitamin D ₃ were excluded from the analysis. Biochemical markers not repeated at t ₂ due to large overall participation drop-out (30% over 2 years)	<u>Treatment group:</u> Significant increase in 25-hydroxy Vitamin D ₃ at t ₁ (p=0.001). Median PTH significantly decreased at t ₁ as compared to placebo group. No significant effect in any other biochemical marker. Increase in BMD in the left (p=0.01) and right (p=0.002) femoral neck. By multiple regression analysis, most prominent effect shown in the left and right femoral neck between t ₀ and t ₁ . No other significant observations at other measurement sites.	Author states that supplementation with 400 IU vitamin D per day in elderly women slightly decreases PTH secretion and increases BMD at the femoral neck.

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Prince R <i>et al.</i> The effects of calcium supplementation (milk powder or tablets) and exercise on bone density on postmenopausal women. <i>J. Bone Miner. Res.</i> 1995; 10:7	Randomized, placebo-controlled trial Measured: Bone density of the lumbar spine (L2 - L4), distal tibia/fibula (ankle), and the hip (femoral neck, trochanter, inter-trochanter site) by DEXA; blood and urine biochemical markers including creatinine, calcium, phosphorus, 25-hydroxyvitamin D, intact PTH, and hydroxyproline.	(N=168) Women aged 50 - 70 years and at least 10 years postmenopausal. Exclusion criteria: significant chronic diseases; received estrogen replacement or other steroid hormones; anticonvulsant drugs; thiazide diuretic drugs, or other medication that would influence calcium metabolism. Other criteria included the following: more than 500 mg calcium tablet supplementation for more than 1 month in the last year or exercise for more than 2 hours per week in the past year.	24 months	<u>Experimental group:</u> Group 1: (N=42) received 1 g elemental calcium as calcium lactate-gluconate tablets (Sandoz, Basel, Switzerland) at bed time. Group 2: (N=42) received 208 ml of skim milk powder per day which contained 1 g elemental calcium at bed time, if possible. Group 3: (N=42) received calcium tablets like group 1, but were asked to exercise for 4 hours per week (at least 2 hours were supervised classes where the primary exercise activity was weight bearing;	Group 2 was asked to reduce their energy intake by 1220 kJ by avoiding high fat foods. Other groups: habitual diet.		As assessed by questionnaire, the participants of the calcium group increased their exercise activity by approximately 10% over the duration of the study. This was statistically significant. Baseline results were comparable in the four groups except for the bone density at the femoral neck and ionized calcium.	A small but significant decrease in non-supplement calcium intake within group 2 (milk powder) was observed. Calcium supplementation in the form of calcium tablet, calcium tablet plus exercise, or skim milk powder prevented bone loss at the trochanter and inter-trochanter, but not in the femoral neck. The percent change at this site was statistically significant from control (P<0.05). Calcium supplementation plus exercise had no extra effect at any other site. No groups lost bone mass in the lumbar spine. Calcium supplementation reduced bone absorption (P=0.02). Serum PTH was also reduced at year one (P=0.03) but not year two. Bone loss at the ankle was less in calcium supplemented groups at the ultra-distal site than placebo (P=0.01), but not in other sites measured in the ankle.	The authors suggest that these data support the implementation of a simple public health regimen to prevent age-related bone loss with calcium supplementation either by calcium tablet or by milk powder. The authors further suggest that the extra effect of exercise plus calcium at the femoral neck suggests a site-specific effect of physical activity on bone density in addition to its possible effect to prevent fracture by muscle strength and coordination.

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				<p>walking for 2 hours per week was the other primary form of exercise).</p> <p><u>Control group:</u> (N=42) received placebo tablets (Sandoz)</p>					

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Reid, IR <i>et al.</i> Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial Am. J. Med. 1995; 98:331	Randomized double-blind placebo controlled trial Measured BMD by DEXA of the whole body, lumbar spine (L2 - L4), and the proximal femur. Vertebral fracture incidence was also measured.	Caucasian women (N=122) ≥ 3 years post menopause	Initial study: 2 years Follow-up: additional 2 years (86 of original 122 subjects)	<u>Control:</u> placebo effervescent tablet <u>Treatment:</u> 1000mg elemental calcium (5.24g calcium gluconate and 0.8g calcium carbonate) effervescent tablet. ½ tablet twice daily Both tablets supplied from Sandoz.	<u>Control:</u> habitual diet + placebo tablet <u>Treatment:</u> habitual diet + 1000mg calcium tablet (½ tablet twice daily) Baseline dietary calcium intake as assessed by questionnaire: Control = 710±300mg/d Treatment = 760±290mg/d			Reduction in the loss rate of BMD in calcium supplemented group throughout 4 year study period (p = 0.002). Total body bone loss significantly less in calcium treated group between study years 2 - 4 (p = 0.02). Lumbar spine bone loss reduced in calcium treated group in year 1 (p = 0.004) and over the entire 4 year period (p = 0.03). Proximal femur BMD was significantly greater over the 4 year study period. Femoral neck (p = 0.03); trochanter (p = 0.01) 9 symptomatic fractures: 7 placebo group, 2 calcium treated group (p = 0.037).	The authors state that calcium supplementation produced a sustained reduction in the rate of loss of the total body BMD in healthy postmenopausal women.

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Ceopollaro, C <i>et al.</i> Effect of calcium supplementation as a high-calcium mineral water on bone loss in early postmenopausal women. <i>Calcif. Tissue Int.</i> 1996; 59:238	Randomly assigned treatment study Measured: BMD at a non-dominant distal radius by peripheral quantitative computed tomography; serum osteocalcin	45 consecutive postmenopausal women aged between 48 and 57 years (mean 52.58±1.99 years) Exclusion criteria: major medical illness, potentially interfering medications, and extremes in height and weight	13±1 months	<u>Treatment 1:</u> 1L/day high calcium (408mg/L Calcium Bicarbonate) mineral water <u>Treatment 2:</u> 1L/day low calcium (80mg/L Calcium Bicarbonate) mineral water	Both treatment groups maintain habitual diets while participating in study			Low calcium group: significant decrease in BMD at the distal radius ($p < 0.001$) Significant difference in BMD between the two treatment groups ($p < 0.05$) High calcium group: significant reduction in osteocalcin serum levels ($p < 0.05$)	The authors suggest that this study provides further evidence to support the use of a high calcium mineral water as an effective prophylaxis against postmenopausal bone loss.

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Fujita, T. Heated Oyster Shell-Seaweed Calcium (AAA Ca) on Osteoporosis. Calcif Tissue Int. 1996;58:226.	Randomized, prospective, double-blind test Measured: lumbar spine and radial bone mineral density at 3 month intervals, PTH, Urinary Ca/Cr, alkaline phosphatase	N=58 elderly, chronically hospitalized women with a mean age of 80, without disease primarily affecting the skeletal system Exclusion criteria: 24 patients with severe compression fracture, marked osteophyte formation in L ₂ -L ₄ as well as severe calcification of abdominal aorta interfering with accurate measurement.	30 months	Group A: (n=20) received 900mg/d Ca as AAA Ca (35% activity level 3, 35% level 2, 30% level 1) Group B: (n=18) 900 mg/d as Calcium Carbonate (33% activity level 3, 28% level 2, 39% level 1) Group C: (n=20) placebo (20% activity level 3, 55% level 2, 25% level 1) Supplements given as 6 capsules in 3 doses at meals.	Regular hospital diet Hospital diet contained 600 mg Ca/d	From the 25 th -30 th month all groups switched to receiving AAA Ca.	Degree of activity classified in 3 grades (3=walking freely without assistance, 2=walking around with assistance, 1=confined to a wheelchair or bed)	From the 6 th to the 24 th month of the study the ratio of lumbar spine BMD to the basal pretest value was consistently and significantly higher in Group A than in Group C but not higher in Group B than in Group C. PTH, measured at 12 months after beginning the study, was lower in Group A than in Group C, but no significant difference was found between Groups B and C. At 3 months after the placebo switched to AAA Ca in Group C, serum PTH was significantly decreased from the level during placebo supplement. Morning urine Ca/Cr decreased in Groups A after 18 months and in B after 12 months but not in C. Serum alkaline phosphatase decreased in Group A significantly compared with Group C, but not in Group B.	The authors conclude that AAA Ca appears to be effective for increasing BMD in elderly subjects.

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Lips, P <i>et al.</i> Vitamin D supplementation and fracture incidence in elderly persons: a randomized placebo controlled clinical trial. <i>Ann. Intern. Med.</i> 1996; 124:400	Randomized placebo controlled clinical trial Measured dietary calcium intake and serum 25-hydroxy vitamin D ₃ in patient subgroup. Hip fractures and peripheral fracture incidence.	1916 female and 662 male subjects at least 70 years of age (mean 80±6 years) Exclusion criteria: history of hip fracture or total hip arthroplasty, known hypercalcemia, sarcoidosis or recent urolithiasis within 5 years.	3.5 year maximum	<u>Control:</u> placebo tablet <u>Treatment:</u> 400 IU Vitamin D ₃ in a single tablet daily	Both treatment groups were advised to supplement their habitual diet with at least 3 servings of dairy products per day to ensure a calcium intake of 800 – 1000mg/day Mean dietary Calcium intake = 868mg/day by dietary questionnaire.		Patients who took medications that influence bone metabolism were not excluded from the trial	Hip fractures: placebo group = 48 Vit. D ₃ group = 58 (p = 0.39, intention-to-treat analysis) Peripheral fractures: placebo group = 74 Vit. D ₃ group = 77 (p = 0.89) Serum Vitamin D ₃ : placebo group = 23 nmol/l Vit. D ₃ group = 60 nmol/L	The authors state that these results do not show a decrease in the incidence of hip fracture or other fractures in Dutch elderly persons after Vitamin D ₃ supplementation

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<p>Lloyd, T. et al.. The effect of calcium supplementation and tanner stage on bone density, content and area in teenage women. Osteoporosis Int. 1996; 6:276.</p>	<p>Randomized, double-masked, placebo-controlled trial</p> <p>Measured: bone mineral content; bone area and bone density</p>	<p>N=112 white girls aged 11.9 ± 0.5 years, premenarchal</p> <p>All subjects had consent from their parents, were between 80% and 120% of ideal weight and height, did not take medication regularly, had no medical history problems known to affect bone development, and had no known dietary disorders.</p>	<p>24 month</p>	<p>Control group: placebo pills (microcrystalline cellulose</p> <p>Supplement group: 500 mg calcium as calcium citrate malate (CCM) per day Given as 2 tablets per day of 250 mg Ca each</p>	<p>Habitual</p> <p>Prospective 3-d diet records completed at baseline and every 6 months thereafter</p>		<p>Compliance was 72% on average for both groups</p> <p>No significant differences were noted between those who dropped out and those who completed the study.</p> <p>Ca intake from dietary sources averaged 983 mg/d for the entire study group</p>	<p>Supplement group had greater increases of total body bone measures: content 39.9% vs. 35.7% ($p=0.01$), area 24.2% vs. 22.5% ($p=0.15$), & density 12.2% vs. 10.1% ($p=0.005$). Region-of-interest analyses showed that the supplemented group had greater gains compared with the controls for bone mineral density, content, & area. In lumbar spine and pelvis, the gains made by supplemented group were 12%-24% greater than the increases made by the control. In subjects with below-median Tanner scores, bone acquisition was not affected by Ca supplementation or dietary Ca level. However, the Ca supplemented subjects with above-median Tanner had higher bone acquisition rates than the placebo group with above-median Tanner scores. Relative to the placebo, the supplemented group had increased yearly gains of bone content, area and density, which represented about 1.5% of adult female values.</p>	<p>The authors conclude that the increases in bone content, area and density in the supplemental group if held to adult skeletal maturity could provide protection against future risk of osteoporotic fractures.</p>

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<p>Mizunuma, H, et. al.. Calcium supplements increase bone mineral density in women with low serum calcium levels during long-term estrogen therapy. <i>Endocrine Journal</i>. 1996; 43:411.</p>	<p>Intervention</p> <p>Measured: lumbar spine BMD</p>	<p>Postmenopausal or oophorectomized women who had been undergoing unopposed estrogen therapy for at least 2 yrs and whose serum Ca level was suppressed to below the normal range. N=19 women who had been continuously taking a dose of 0.625 mg of conjugated estrogen (CEE; Premarin) for at least 2 years.</p> <p>Risks and benefits of unopposed estrogen therapy were explained and all gave informed consent. None had evidence of bone disease or a medical condition that would predispose to bone loss.</p>	<p>2 years</p>	<p>N=19 divided into 2 groups according to their serum calcium level. Group 1: (CEE+Ca) The normal range at the hospital is 8.9-10.1 mg/d so a daily dose of 600-800 mg of calcium lactate was administered in an attempt to correct serum calcium levels to women whose serum calcium levels decreased below 8.9 mg/dl for CEE therapy.</p> <p>Group 2: (CEE) Those with serum Ca (≥ 9.0 mg/dl) were diagnosed as normocalcemia and treated with the same dose of CEE for another 2 years.</p>	<p>Habitual Diet</p>		<p>N=7 had spontaneous menopause</p> <p>N=12 had hysterectomy with (10 women) or without (2 women) bilateral oophorectomy for benign gynecologic diseases.</p> <p>None were receiving gestagen (which is recommended to women with an intact uterus) because they did not want genital bleeding.</p>	<p>Lumbar spine BMD decreased by -0.37% for 2 years in women treated with estrogen alone, while that of women treated with estrogen and calcium increased by 2.78% ($p=0.003$).</p>	<p>The authors conclude that these results indicate that low dose calcium supplements potentiate the effect of estrogen in women with decreased serum calcium during long-term hormone replacement therapy.</p>

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Recker, R.R. et al.. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. Journal of bone and mineral research. 1996; 11:1961.	Prospective, randomized, double-blind, placebo-controlled trial Measured: spine fracture incidence and forearm bone mass changes	N=197 Healthy white elderly women aged 73.5 ± 7.1 years in mostly rural communities, living independently and consuming <1 g/d Ca No upper age limit. Exclusions: those with other diagnoses or with treatments known to affect the skeleton	4.3 ± 1.1 years	Four groups as follows: 1) PF-calcium Prevalent fracture + supplement of 600 mg Ca carbonate / day 2) PF-placebo Prevalent fractures + placebo pill 3) NPF-calcium No prevalent fractures + 600 mg/d Ca 4) NPF-placebo No prevalent fractures + placebo pill Prevalent spine fractures (PF): n=94 No Prevalent spine Fractures (NPF): n=103 Not randomized based on prevalent fracture status.	Usual calcium intake were <1 g/d Ca intake at baseline estimated based on an abbreviated questionnaire administered by the research nurse in charge of the project		N=750 screened but only n=251 entered the study Those excluded had calcium intake levels >1 g/d, some chose not to participate, some excluded because they only complied for 1 year, death, or moved out of area	In the PF group, 15 of 53 subjects on calcium had incident fractures, compared with 21 of 41 on placebo ($p=0.023$). Ca did not reduce the rate of incident fractures in the NPF group. Those with a prevalent fracture on entry and not treated with Ca were 2.8 times more likely to experience an incident fracture than all others. Change in forearm bone mass on placebo in the PF group was $-1.24 \pm 2.41\%$ /year compared with $+0.31 \pm 1.80\%$ /year on Ca (<0.001). In the NPF group, the difference was less $-0.39 \pm 2.08\%$ /year vs. $0.00 \pm 1.64\%$ /year ($p=0.2$).	The authors conclude that in elderly postmenopausal women with spine fractures and self-selected calcium intakes of <1 g/d, a calcium supplement of 1.2 g/d reduces the incidence of spine fractures and halts measurable bone loss.

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<p>Bonjour, J-P <i>et al.</i> Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind placebo-controlled trial. <i>J. Clin. Invest.</i> 1997; 99:6</p>	<p>Randomized double-blind placebo-controlled trial</p> <p>BMD, BMC, and bone size by DEXA of the distal radial metaphysis, radial diaphysis, femoral neck, femoral trochanter, femoral diaphysis, lumbar spine (L2 - L4).</p>	<p>149 healthy prepubertal Caucasian girls (mean age = 7.9±0.1 years)</p> <p><u>Exclusion criteria:</u> no parental approval, ratio weight/height less than 3rd or greater than 97th percentile according to Geneva reference values, physical signs of puberty, chronic disease, gastro-intestinal disease, congenital or acquired bone disease, or regular use of medications.</p>	<p>48 weeks</p>	<p><u>Control:</u> placebo food products identical to the treatment group without calcium enrichment.</p> <p><u>Treatment:</u> calcium enriched food products including chocolate cakes (516 mg/serving); caramel cakes (512 mg/serving); biscuits (548 mg/serving); fruit juices (383 mg/serving); powdered drink chocolate (530 mg/serving); chocolate bars (429 mg/serving); yogurts (478 mg/serving).</p> <p>On average, the intake of two calcium-enriched food products per day provided about 850mg.</p>	<p>Both groups maintained habitual diet with the addition of two food products (placebo or calcium-enriched) per day.</p>			<p>Radial diaphysis BMD significant gain (Calcium group, $p < 0.02$). Femoral neck not significant in either group. Femoral trochanter BMD significant gain (Calcium group, $p > 0.05$). Femoral diaphysis BMD significant gain (Calcium group, $p < 0.01$). Radial metaphysis not significant in either group. Lumbar spine not significant in either group.</p> <p>At all sites, the mean increment in bone mass was greater in the Calcium group than placebo group.</p> <p>Mean increases in both BMC and bone area were also greater in the Calcium group than placebo group (not statistically significant). Mean BMD positively correlates to the cumulative amount of calcium ingested from enriched foods ($r = 0.24$, $p = 0.038$, $n=77$)</p>	<p>The authors state that calcium enriched foods significantly increased bone mass accrual in prepubertal girls with a preferential effect in the appendicular skeleton, and a greater benefit to those with a lower spontaneous calcium intake.</p>

Literature Citation	Study Design	Number and Description of Subjects	Duration of Study	Specifics of Intervention Including Source and Identity of Test Material	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Cadogan, J et. al.. Milk intake and bone mineral acquisition in adolescent girls: randomized, controlled intervention trial. BMJ 1997; 315:1255	Randomized controlled intervention trial Measured: bone mineral density; bone mineral content	N=82 white girls aged 12.2 (SD 0.3) years recruited from 4 secondary schools in Sheffield No history of bone disease, no drugs taken to influence calcium metabolism, all non smokers, none were taking calcium supplements, no special diet regiments	18 months	Milk group: 568 ml (1 pint) of whole or reduced fat milk per day (type of milk depended on subjects preference) Milk delivered daily to subjects home. Subjects asked to consume as much of the pint as possible each day along with their normal food intake. Control group: continue their habitual diet	Habitual diet Nutrient intake assessed at baseline and at the end of the study using 7 day weighed intake method (subjects weighed and recorded all items they ate and drank for 7 days)		Calcium contents of whole, semi-skimmed, and skimmed milk are virtually the same: 115 mg / 100g, 118 mg / 100 g, and 120 mg / 100 g respectively. The subjects that dropped out were not different from the other subjects but dropped out for the following reasons. N=1 excluded from milk group because of non-compliance N=1 excluded from control group due to moving to a new school Most in milk group chose semi-skimmed milk. N=6 chose whole milk. N=2 chose skimmed milk.	N=80 completed the trial At baseline daily milk intake averaged 150 ml in both groups. On average the intervention group consumed an additional 300 ml a day throughout the trial. Intake of milk in the control group remained relatively the same (142 ml at baseline, 160 ml at study end). Compared with the control group, the intervention group had greater increases of bone mineral density (9.6% v 8.5%, P=0.017; repeated measures analysis of variance) and bone mineral content (27% v 24.1%, P=0.009). No significant differences in increments in height, weight, lean body mass, and fat mass were observed between groups. Bone turnover was not affected by milk supplementation. Serum concentrations of insulin-like growth factor I increased in the milk group compared with the control group (35% v 25%, P=0.02).	The authors conclude that increased milk consumption significantly enhances bone mineral acquisition in adolescent girls and could favorably modify attainment of peak bone mass.

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Dawson-Hughes, B <i>et al.</i> Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. <i>NEJM</i> 1997; 337:10	Double-blind placebo controlled trial Measured: BMD of hips, spine, and total body measurements by DEXA. Serum 25-hydroxy-vitamin D; serum 1,25-dihydroxyvitamin D; serum PTH; serum osteocalcin; serum Ca ²⁺ Urinary calcium, creatinine, and N-telopeptide cross-links	445 subjects (199 men, 246 women) Demographics: 430 Whites, 11 Blacks, and 4 Asians. <u>Exclusion criteria:</u> current cancer, hyperthyroidism, kidney stone (within 5 years); renal disease; bilateral hip surgery; bisphosphate therapy; calcitonin, estrogen, tamoxifen, or testosterone treatment in the past 6 months, or fluoride in the past 2 years; femoral neck $2 \leq \text{BMD} \leq 2 \text{ SD}$ for subjects the same age and sex; dietary calcium exceeding 1500mg/day; laboratory evidence of liver or kidney disease.	3 years	<u>Control:</u> Placebo (microcrystalline cellulose) <u>Treatment:</u> 500mg elemental calcium (calcium citrate malate) and 700 IU Vitamin D3 (cholecalciferol) in two separate tablets Tablets provided by Procter and Gamble	Both treatment groups maintained their habitual diets (avoiding supplemental calcium and vitamin D two months prior and throughout the trial)		56 subjects dropped-out	Treatment group: BMD significant positive effect as compared to placebo group. Femoral neck ($p = 0.02$, all subjects); Lumbar spine (L2 - L4, $p = 0.04$, all subjects); total body ($p = 0.001$, all subjects) Female subjects had significantly less total body bone loss as compared to the placebo group ($p < 0.001$). No significance at other measured sites. Adjustments based on baseline BMD and CI did not alter these results. 37 observed non-vertebral fractures: 26 fractures in placebo group, 11 Ca-VD3 treated group ($p = 0.02$).	The authors state that in men and women age 65 years or older, dietary supplementation with calcium and vitamin D moderately reduced bone loss in the femoral neck, lumbar spine, and total body while reducing the non-vertebral fracture incidence rate.

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Devine, A et. al. A 4-year follow-up study of the effects of calcium supplementation on bone density in elderly postmenopausal women. Osteoporosis Int. 1997; 7:23.	Follow-up of a randomized, double-masked, placebo-controlled trial Measured: Changes in bone density at the lumbar spine, hip and ankle sites and current Ca intake	N=84 elderly women aged 54-74 years that were more than 10 years postmenopause were available for the follow-up study N=128 in the original 2 year study	4 years	Placebo Group (Control): n=21 No calcium supplements at all Calcium Supplement Group: n=14 Took 1 g Ca supplement (calcium lactate gluconate) per day (taken at night) Non-Compliant Group: n=49 Took calcium supplements (1 g/d) for 2 years and then stopped taking them.	Habitual diet		N=84 available for follow-up self-administered questionnaire on compliance of supplementation of Ca tablets between years 2 and 4 of the study N=44 declined to continue, were not able to be contacted, or enrolled in a new trial. The subjects that dropped out after 2 years were not different from the other subjects.	Over the 4 years the calcium supplement group (mean Ca intake of 1988 ± 90 mg / d) did not lose bone at the hip and ankle site. The control group (mean Ca intake of 952 ± 109 mg/d) lost significantly more bone than the Ca supplemented group at all sites of the hip and ankle. No overall bone loss was seen at the spine, in either group, over the 4 years. Between years 2 and 4 the non-compliant group (mean Ca intake of 981 ± 75 mg/d) lost significantly more bone at all sites of the ankle than the Ca supplement group. In all subjects the 2 yr change in bone density was significantly correlated with the change in total Ca intake measured between yr 2 and 4 at the mid-tibial ($r=0.38$, $p<0.005$), ultradistal tibial ($r=0.41$, $p<0.005$) and the lumbar spine ($r=0.30$, $p<0.05$).	The authors conclude that calcium supplementation produces a sustained reduction in the rate of loss of bone density at the ankle and hip sites in elderly postmenopausal women. The authors also conclude that increasing dietary calcium intake in women should be the aim of a public health campaign.

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Graafmans, WC <i>et al.</i> The effect of vitamin D supplementation on the bone mineral density of the femoral neck is associated with vitamin D receptor genotype. J. Bone Miner. Res. 1997; 12:8	Placebo-controlled clinical trial Measured: BMI; Daily dietary Calcium intake by questionnaire ; BMD by DEXA of Right and Left femoral neck; serum and urine biochemical markers; vitamin D receptor genotyping by direct haplotyping using PCR of RFLPs.	81 women at least 70 years of age (mean age = 78±5 years) Exclusion criteria: cognitive impairment, non-continuous residency to area, lower extremity fracture during trial period.	2 years	<u>Control:</u> placebo tablet taken daily <u>Treatment:</u> vitamin D supplement (400 IU) tablet taken daily	<u>Control:</u> habitual diet + placebo <u>Treatment:</u> habitual diet + vitamin D tablet			Difference in BMD in response to Vitamin D supplementation not significantly related to baseline 25-hydroxy vitamin D ($p = 0.10$), 1,25-dihydroxy vitamin D ($p = 0.10$), or baseline BMD values ($p = 0.75$) Body weight significantly related to Δ BMD ($p < 0.01$), but did not alter relationship between use of vitamin D and Δ BMD Δ BMD statistically significant greater in both the BB and Bb genotypes ($p = 0.03$) Δ Osteocalcin significantly different in the the bb genotype Adjustments for age, age at menopause, BMI, and dietary calcium intake did not change the relationship between BMD and genotype.	The authors state the following: the VDR genotype-dependent effect of Vitamin D supplementation in these elderly subjects suggests a functional involvement of VDR gene variants in determining BMD.

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Komulainen, M et. al.. Vitamin D and HRT: No benefit additional to that of HRT alone in prevention of bone loss in early postmenopausal women. A 2.5 year randomized placebo-controlled study. Osteoporosis Int. 1997; 7:126.	Randomized placebo-controlled study Measured: Lumbar (L1-4) and femoral neck BMD	Non-osteoporotic postmenopausal women. Study population was a subgroup of the Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE) (n=13100) N=464 early postmenopausal women Exclusions: those women who wanted to change treatment groups; history of breast or endometrial cancer; thromboembolic diseases; medication-resistant hypertension	2.5 years	1) HRT: a sequential combination of 2 mg estradiol valerate (days 1-21) and 1 mg cyproterone acetate (days 12-21) and a treatment free interval (days 22-28) (E ₂ Val/CPA) 2) Vitamin D ₃ : cholecalciferol at 300 IU/day + 93 mg Ca ²⁺ /day with no intake during June-August 3) HRT + Vit D: Treatments 1 and 2 combined 4) Placebo: calcium lactate at 500 mg/day (equivalent to 93 mg Ca ²⁺ /day) Randomized by a computer program	Habitual Postal inquiry sent to collect dietary habits and collected at baseline by a nurse. Daily dietary Ca intake based on consumption of milk products and calculated as the sum of Ca intake from milk, sour milk, yoghurt (120 mg/dl) and cheese (87 mg/slice). Number of meals containing fish were recorded monthly.		N=391 (84%) completed the study but only n=388 included in the final analysis N=73 dropouts for various reasons: menstrual disorders such as hypermenorrhoea, dysmenorrhoeal or metrorrhagia, headache, lumbar and femoral BMD more than 2 SD below the mean, interruptions in HRT exceeding 6 months, BMD measurements of poor quality. The women in this study were not different from those that left the study according to baseline characteristics.	After 2.5 years of treatment lumbar BMD had increased by 1.8% in the HRT group (p<0.001) and by 1.4% in the HRT + Vit D group (p=0.002), whereas lumbar BMD had decreased by 3.5% (p<0.001) in the Vit D group and by 3.7% (p<0.001) in the placebo group. The loss of femoral neck was lower in the HRT (-0.3%) and the HRT + Vit D (-0.9%) groups compared with the Vit D (-2.4%) and the placebo groups (-3.7%).	The authors conclude that this study confirms the beneficial effect of HRT on BMD. It also shows that low-dose vitamin D supplementation has only a minor effect in the prevention of osteoporosis in non-osteoporotic early postmenopausal women and does not give any benefit additional to that of HRT alone.

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Nowson CA <i>et al.</i> A co-twin study of the effect of calcium supplementation on bone density during adolescence. <i>Osteoporosis Int.</i> 1997; 7:219	Randomized co-twin, placebo-controlled, double-blind intervention study. Measured: BMD of the lumbar spine (L2 - L4), total hip, femur neck, Ward's triangle, and forearm by DEXA. Total body mineral content (BMC), forearm BMC and total body soft tissue composition (lean mass and fat mass) were also measured by DEXA.	55 female twin-pairs aged 10 - 17 years (mean age = 14) enrolled with the Australian National Health and Medical Research Council	18 months	<u>Experimental group:</u> 1000 mg/day effervescent calcium tablet (Sandocal 1000, Sandoz) containing 0.8 g per tablet calcium carbonate and 5.23 g per tablet calcium lactogluconate. <u>Control group:</u> placebo tablet of similar taste, appearance and composition to the calcium supplement. <u>Protocol:</u> All pairs were matched for menarchial status at baseline (74% were post-menarchial).	Habitual diet. Placebo group baseline dietary calcium intake (mean±SD): 692.3±253.7 mg as assessed by four day food record. Experimental group baseline dietary calcium intake: 776.1±318.7 mg as assessed by four day food record.		9 pairs dropped out within 1 month, and 4 pairs took less than 4 months of supplements. The authors did not state if this withdrawal affected the study. Reasons for withdrawal included: disliked supplement taste, found requirements too demanding, family circumstance changes, and perceived gastrointestinal discomfort. 42 pairs (22 monozygotic, 20 dizygotic; including one monozygotic pair from a set of triplets) completed at least 6 months of the intervention. 37 completed 12 months; 28 pairs completed 18 months.	Independent of age, calcium supplementation was associated with a greater increase in BMD at the spine (1.5%, P<0.01) and at the total hip (1.3%, P<0.01) at the 6 month interval. From baseline to 18 months, a greater within-pair difference in BMD was observed in the spine (P<0.05), but not in the hip or the femoral neck. The effect of calcium supplementation on bone density was assessed compared to placebo over the combined time interval. There were no differences in the within-pair changes in BMD after the first 6 months. This finding was confirmed by mathematical modeling. No covariates were shown to be associated with the within-pair differences in BMD.	The authors conclude that after 18 months of supplementation, an increase in BMD at the spine was observed in females with a mean age of 14 years. This effect was seen in the first 6 months; thereafter, there was no accelerated increase in bone density. The subsequent analysis after 3 years, follow-up and continuance of the study, until the attainment of peak bone mass will be important in clarifying the size of the intervention effect, optimal timing for increased calcium intake, and the long term effects of this intervention.

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Bæcksgaard, L <i>et al.</i> Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. <i>Osteoporos. Int.</i> 1998; 8:255	Randomized, double-blind placebo-controlled trial Measured: BMD of the lumbar spine (L2 – L4), hips, and forearm by DEXA; Calcium and Vitamin D intake assessed by dietary diary; Serum Calcium, Phosphate, and intact PTH	240 healthy postmenopausal Caucasian women ages 58 – 67 years (mean age = 62.5 years) Exclusion criteria: treatment with oestrogen or calcitonin (past 12 months); treatment with bisphosphates (past 24 months); disease states known to affect bone metabolism; renal disease with serum creatinine > 120µmol/L; hepatic disease with increased ALAT and/or decreased extrinsic coagulation factors II, VII, and X	2 years	<u>Control:</u> (N=80) placebo tablets <u>Treatment 1:</u> (N=80) Calcium (1000mg calcium carbonate) and Vitamin D (14ug or 560 IU) supplements in the form of two tablets <u>Treatment 2:</u> (N=80) Supplementation regimen identical to treatment 1 with the addition of a multivitamin. Supplements in the form of two tablets All tablets provided by Lube Ltd	All treatment groups maintained habitual diets		For all parameters, the authors observed no significant difference between treatment groups 1 and 2. Therefore, these two groups are combined as a single treatment group.	Lumbar spine (L2 – L4) Significant increase ($p < 0.0001$) in BMD in year 1. Overall increase 1.6% ($p < 0.002$). Statistically significant difference (increase) in BMD between treatment and placebo groups at both year 1 and 2. Distal forearm No significant changes from baseline in either group. Serum Calcium Statistically significant difference ($p < 0.0001$) between treatment and placebo at both year 1 and 2. Serum PTH Statistically significant differences between baseline in treatment group and placebo group at year 1 ($p < 0.0001$) and year 2 ($p < 0.001$).	The authors state that together with significant changes in serum calcium and PTH, indicates that a long-term calcium and vitamin supplement increases intestinal calcium absorption.

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Renner, E. et al.. Bone mineral density of adolescents as affected by calcium intake through milk and milk products. Int Dairy Journal, 1998; 8:759.	Dietary intervention Measured: bone mineral content and density	N=190 adolescents (n=113 females, n=77 males)	1 year	1) Intervention group: bone mineral values were below average. Received enough milk and milk products to supply 1000mg/day of Ca. Chose products from a list and were given exact amount of each to provide the required amount of Ca and were advised on how the products could be best integrated into the diet. 2) Control group: bone mineral values below average, no dietary intervention. 3) Medium group: average bone mineral values, no dietary intervention: a second control group. 4) Optimum	Ca intake through milk and milk products determined using FFQ and 24 hr recall		N=129 (n=76 female, n=53 male) took part in follow-up exam after 1 year. There were no reasons listed for drop outs.	Bone mineral density was significantly improved by about 50% when compared with control subjects without such dietary intervention (+0.053 vs. +0.036g cm ⁻²). The rate of increase, however, was significantly lower for girls than for boys (also about 50%: +0.019 vs. +0.038 ⁻²), possibly due to the more advanced bodily development of girls at this age.	The authors conclude that as the rate of increase of the bone mineral density is significantly decreasing for adolescents of this age (20-35% in boys 16 yr of age when compared with 15 yr olds, and 40-50% in girls), it can be predicted that such a dietary intervention starting at 15 yr of age will lead to an avg. level of bone mineral values after 3-4 yr and even to optimum levels after 6-7 yr in boys with an originally sub-average level. However, such improvement is no longer feasible for girls at this age. The concentration of osteocalcin and PTH as well as the activity of alkaline phosphatase in blood serum indicated that the higher than proportional increase of bone mineral density in the intervention group can be attributed to a decreased bone turnover which was caused by an

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				group: bone mineral values above average, no dietary intervention, a third control group.					increased intake of Ca through milk and dairy products.

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Ricci, TA <i>et al.</i> Calcium supplementation suppresses bone turnover during weight reduction in postmenopausal women. <i>J. Bone Miner. Res.</i> 1998; 13:6	Randomized, double-blind placebo-controlled trial Measured: Biochemical markers of bone re-sorption (urinary pyridinium cross-links) and bone formation (serum osteocalcin and PTH); Total body BMD; Fat Mass (FM); Lean soft tissue mass (LM); serum sex hormone binding globulin (SHBG); serum insulin-like growth factor (IGF-I); serum 25-hydroxy vitamin D	43 obese postmenopausal (3 years since menopause) with BMI range 28 – 42 and low to moderate calcium intake (< 800mg/day) All subjects were participants in a concurrent 6 month behavior-modification, nutrition-education weight-loss program Exclusion criteria: currently taking medications; disease states known to affect bone metabolism	6 months	<u>Control:</u> (N=21) placebo tablets (one tablet/day) <u>Treatment:</u> (N=22) 1000mg calcium citrate malate tablets (2 500mg tablets one tablet taken with morning and evening meals) All tablets provided by Proctor and Gamble	All subjects were on a reduced energy diet according to a behavior modification, nutrition-education weight-loss program. All subjects were asked not to take vitamin/mineral supplements two weeks prior and throughout the study.		12 participants dropped out of the study.	Weight loss: both groups lost a similar amount of weight After weight loss: Loss of BMD greater in the placebo group by 1.4% (p < 0.08) after weight loss. Pyridinium cross-links increase in the placebo group (p < 0.05) after weight loss Osteocalcin increased in the placebo group (p < 0.05) SHBG increased 42% in both groups (p < 0.01) PTH increased 34% in calcium treatment group (p < 0.01) During weight loss: Calcium supplement suppressed urinary DPD (p < 0.05) and osteocalcin (p < 0.01); suppressive effect on PTH (p < 0.05)	The authors state that 1 gram per day of calcium supplementation normalizes the increased calcium-PTH axis activity and elevated bone turnover rate observed during moderate voluntary energy restriction in postmenopausal women.

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Riggs, LB et al Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. J. Bone Miner. Res. 1998; 13:2	Randomized double-blind placebo-controlled trial Measured: Serum 25-hydroxy vitamin D (baseline only), urinary free pyridinoline (baseline, 1yr, 4yr), serum phosphate, creatinine, alkaline phosphatase, urinary creatinine, serum osteocalcin, bone alkaline phosphatase isoenzyme, free pyridinoline cross-links, intact PTH, 1,25-dihydroxy vitamin D BMD lumbar spine, proximal femur, and total body.	236 fully ambulatory postmenopausal (menopause \geq 10 years) women ages 61 – 70 years. Exclusion criteria: renal lithiasis, impaired renal function, hypercalcemia, hypercalcuria ($>$ 300mg/24h), known disease state that affects bone metabolism, oestrogen treatment, vitamin D or calcium treatment, or other known drugs that affect bone, use of bisphosphates or fluoride	4 years	<u>Control:</u> (N=117) Placebo tablets <u>Treatment:</u> (N=119) elemental calcium (calcium citrate) tablets taken 4 times daily. Dosage: 1600mg/day	Habitual diet Dietary calcium for both groups was ~715mg/day.		59 participants dropped out of the study.	Fracture incidence: No significant difference between groups in vertebral or non-vertebral fractures. Values shown as a difference (treatment – placebo) of the net change (follow-up as a percent of baseline). Lumber spine BMD difference 2% at year 1 ($p < 0.001$) and 0.3% at year 4 (not significant). Proximal femur BMD difference 1.3% at year 1 ($p = 0.003$) and 1.3% at year 4 ($p = 0.015$). Total body BMD difference 0.4% at year 1 ($p = 0.002$) and 0.9% at year 4 ($p = 0.017$). Serum PTH 18.9% ($p = 0.002$) Serum Osteocalcin -11.9% ($p = 0.003$) Serum free pyridinoline -32.2% ($p = 0.003$)	The authors conclude that due to their safety, high tolerance, and low expense, calcium supplements may be use preventative measure for elderly postmenopausal women whose BMD values are normal for their age.

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Storm, D et. al.. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women: A randomized placebo-controlled trial. Journal of Clinical Endocrinology and Metabolism, 1998; 83:3817.	Randomized placebo-controlled trial CaCO ₃ and Placebo groups were double-blinded. The Dietary -D group was open-label but blinded to the PI, dual x-ray absorptometry technician, and the data collectors. Measured: calcium intake; trochanteric bone loss; femoral neck BMD; serum 25-OH vitamin D; PTH	N=60 older postmenopausal women without osteoporosis Inclusion: age over 65 yr, no antiosteoporosis treatments in last 10 yr, t scores of the femoral neck (FN) that were higher than B2.5, good overall health, complete living independence, Ca intake < 800mg/day as measured by FFQ, no plans to travel south of the Mason-Dixon line during 2 consecutive winter seasons; agreed to be randomized into 1 of 3 groups and withhold any vitamin supplementation Exclusion: osteoporotic fractures, diabetes mellitus, renal insufficiency, recent malignancy, congestive heart failure.	2 years	Dietary milk supplementation (Dietary-D): N=20 age 71 ± 1.2 four 8 ounce glasses of milk/day Calcium carbonate (CaCO ₃): N=20 age 72 ± 1.1 - 500mg tablet of CaCO ₃ taken twice per day with meals (1000mg total per day) Placebo (P): N=20 age 71 ± 1.0 Used a CaCO ₃ -matching placebo supplement taken twice per day with meals	Habitual diet FFQ and 4 day food records provided at baseline		Thiazide use and smoking were not exclusionary. N=53 completed the study The subjects that dropped out were not different from the other subjects but dropped out for the following reasons. N=3 drop outs in P group due to gastrointestinal side effects and concurrent illness. N=1 drop out in D group because of refusal to participate N=3 drop outs in CaCO ₃ group because of myocardial infarction, moved out of state, spouse illness.	After 2 yr, P-treated women consumed mean of 683 mg/day of Ca and lost 3% of their trochanterio (GT) bone mineral density (BMD) (P<0.03 vs. baseline). D-treated women averaged a Ca intake of 1028 mg/day and sustained minimal loss from the GT (-1.5%; P=0.30), whereas CaCO ₃ treated women (total Ca intake, 1633 mg/day) suffered no bone loss from the GT and showed a significant increase in spinal and femoral neck BMD (P<0.05). Femoral bone loss occurred exclusively during 2 winters of the study (i.e. total loss, -3.2%, P<0.02 in P-treated women) with virtually no change in GT BMD during summer. Serum 25-OH vitamin D declined by more than 20% (P<0.001) in all groups during winter months but returned to baseline in summer; PTH levels rose ~20% (P<0.001) during winter but did not return to baseline during summer. Urine N-telopeptide and osteocalcin levels increased significantly but only in the P-treated women and only during winter.	The authors conclude that calcium supplementation prevents bone loss in elderly women by suppressing bone turnover during the winter when serum 25-OH vitamin D declines and serum PTH increases. The precise amount of calcium needed to preserve BMD in elderly women requires further study, although in this study, at least 1000 mg/day of supplemental calcium was adequate prophylaxis against femoral bone loss.

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Tupparinen, MT <i>et al.</i> Does vitamin D strengthen the increase in femoral neck BMD in osteoporotic women treated with estrogen. <i>Osteoporos. Int.</i> 1998; 7:32	Prospective, partly randomized study Measured: BMD of the lumbar spine (L1-L4) and the femoral neck (investigators blind to treatment allocation)	60 osteoporotic women (mean age = 55.4 years) All women were a subgroup of a concurrent study, the population-based Kuopio Osteoporosis Risk Factor and Prevention Study (OSTPRE, N=13,100 women with BMDs more than 2 SD below population mean at LS and Femoral neck)	4 year	<u>Control:</u> (N=16) untreated, participants refused treatment, non-randomized group <u>Treatment 1:</u> HRT (2mg estradiol valerate/day, days 1-21 and 1mg cyproterone acetate/day, days 21-28) <u>Treatment 2:</u> HRT + Vitamin D (HRT same as above with the addition of Vitamin D ₃ 300 IU/day and elemental calcium 93mg/day) Subjects were randomized between treatments 1 and 2.	Habitual diet		46 participants dropped out or were excluded from the present study analysis.	Lumbar spine Year 1: BMD increased 5.4% ($p < 0.001$) in treatment group 1 (HRT only) as compared to control. BMD increased 3.7% ($p < 0.001$) in treatment group 2 (HRT + Vit. D) as compared to control. Both groups differed significantly from control ($p < 0.0001$) Year 4: significant increase (treatment 1 $p < 0.05$; treatment 2 $p < 0.01$) in BMD of both treatment groups as compared to control. However, no significant difference was observed between treatment groups. Femoral Neck Year 4: treatment 2 5.8% increase that was statistically different ($p < 0.01$) as compared to control. Fracture incidence data were insufficient for the evaluation of the effects of different treatments.	The authors conclude that estrogen can substantially increase lumbar bone mass in patients with postmenopausal osteoporosis. In addition, they suggest that the combination of HRT and Vitamin D ₃ may increase femoral neck BMD in osteoporotic women than estrogen alone.

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Kreig, MA <i>et al.</i> Effect of supplementation with vitamin D ₃ and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study. <i>Osteoporos. Int.</i> 1999; 9:483	Randomized open controlled study. Measured: QUS of the calcaneus by BUA and SOS; fasting serum calcium, phosphate, 25-hydroxy vitamin D, PTH, Alkaline Phosphatase, and creatinine	248 women (age 62 – 98 years). Mean age 84.5±7.5 years.	2 years	<u>Control:</u> (N=124) untreated <u>Treatment:</u> (N=124) 500mg calcium (1250mg calcium carbonate and 400 IU Vitamin D ₃). One tablet taken twice daily. Treatment tablets were provided by Novartis	Habitual diet		145 participants could not be followed-up. The authors report that there was no measured difference in any parameter between treated subjects and control subjects.	Experimental treatment resulted in significant increases in 25-hydroxy vitamin D by 125% (p < 0.01); decreased PTH by 18% (p < 0.05) and alkaline phosphatase by 15% (p < 0.01). Significantly decrease 25-hydroxy vitamin D (p < 0.01) and increased PTH values (p < 0.01) were observed in the control group. BUA increased significantly in the treatment group (p < 0.05), but decreased in the control group (p < 0.01). Significant difference between control and treatment after 2 years was 3.9% (p < 0.01).	The authors conclude that BUA not SOS reflected a positive effect on bone under supplementation with calcium and vitamin D3 in a population of elderly institutionalized women.

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<p>Kyriakidou-Himonas M <i>et al.</i> Vitamin D supplementation in postmenopausal black women. <i>J. Clin. Endo. Metab.</i> 1999;84:11.</p>	<p>Longitudinal trial.</p> <p>Measured: serum PTH; serum 25-hydroxy vitamin D, 1,25-dihydroxy vitamin D; nephrogenous cAMP; serum calcium and phosphorus; urinary N-telopeptide and creatinine.</p>	<p>(N=10) Healthy African-American women aged 60 – 80 years.</p> <p>Exclusion criteria were not stated.</p>	<p>12 weeks</p>	<p><u>Experimental group:</u> N=10, All subjects received 10 µg vitamin D₃ tablets twice daily.</p> <p>The source of the tablets was not stated.</p> <p><u>Control group:</u> none.</p>	<p>Habitual Diet with instructions to avoid vitamin supplements.</p> <p>Mean daily dietary calcium intake was 400±250 mg/day.</p>		<p>4 of 10 Serum baseline PTH levels were above the kit manufacturer's normal range.</p>	<p>Serum PTH and nephrogenous cAMP levels declined significantly with treatment (p<0.0001 and p<0.01, respectively).</p> <p>Serum 25-hydroxy vitamin D levels declined significantly (p<0.0001).</p> <p>Serum 1,25-dihydroxy vitamin D levels declined significantly (p<0.02).</p> <p>No changes were observed in the serum calcium or phosphorus.</p> <p>N-telopeptide/creatinine ratio declined by 21%, but significance of this decline was not stated.</p>	<p>The authors conclude that their findings should spur further investigation of the use of vitamin D supplementation in the prevention of osteoporosis in the female African-American population.</p>

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Prestwood KM <i>et al.</i> Low dose estrogen and calcium have an additive effect on bone resorption in older women. J. Clin. Endocrinol. Metab. 1999;84:1	Randomized, controlled open label study. Measured: biochemical markers of bone formation including osteocalcin, bone alkaline phosphatase, and type I procollagen peptide; biochemical markers of bone resorption including urinary cross-linked N-telopeptide, C-telopeptides, free deoxypryridinoline cross-links; serum PTH, 25-hydroxy and 1,25-dihydroxy vitamin D; other biochemical markers including serum Ca, phosphorus urinary Ca.	(N=50) Women aged 70 years or more from the Hartford, CT area. Exclusion criteria: current disease state or treatment with medication know to affect bone metabolism, diseases that would prohibit estrogen or calcium therapy. 5 women were excluded from this study.	36 weeks	<u>Experimental groups:</u> Group 1. (N=15) received 12 weeks of 1500mg/day calcium carbonate and 800 IU/day vitamin D followed by 12 weeks of Calcium and vitamin D plus 0.5 mg/day micronized 17 β -estradiol (E_2). Group 2. (N=16) received 12 weeks 0.5 mg/day E_2 followed by 12 weeks of E_2 plus 1500 mg/day calcium carbonate and 800 IU/day vitamin D. <u>Control group:</u> (N=14) did not receive any treatment. The use of placebo in this group was not stated.	Habitual diet. Mean dietary calcium intake at baseline ranged between 127 – 1656 mg/day.		Three subjects withdrew from the control group for reasons not stated. The authors did not state if these dropouts were significantly different from those who remained in the study.	In treatment group 1, bone resorption markers declined (13 – 35%) and bone formation markers also declined (13 – 21%) after 12 weeks of Ca+Vitamin D treatment. The addition of E_2 in this group in a further reduction (11 – 22%) of all bone resorption markers except urinary N-telopeptide x-links and a small reduction in osteocalcin and bone alkaline phosphatase. All markers returned to baseline after 12 weeks treatment cessation except serum N-telopeptide x-links. In treatment group 2, E_2 was associated with decreases (14 – 26%) in N-telopeptide x-links, free deoxypryridinoline x-links, and C-telopeptide x-links without changes in bone formation markers. The addition of Ca+Vitamin D to this treatment group resulted in a further decrease in the bone resorption markers.	The authors conclude that these results suggest that there is an additive effect of low dose estrogen and calcium on bone resorption, but not on bone formation, in older women. The authors further conclude that the combination of low dose estrogen plus calcium is likely to be more effective in older women than either treatment alone.

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				E ₂ tablets were obtained as the Bristol-Meyers-Squibb product labeled Estrace.					

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Dawson-Hughes, B <i>et al.</i> Effect of withdrawal of calcium and vitamin D supplements on bone mass in elderly men and women. <i>Am. J. Clin. Nutr.</i> 2000; 72:745	Randomized, placebo-controlled trial follow-up <u>Measured:</u> Medical history for medications that affect bone metabolism, vitamin/mineral supplements, and number of cigarettes in previous 12 months; Dietary calcium and vitamin D by questionnaire; physical activity scale for the elderly; weight, height; non-vertebral fractures; BMD of femoral neck, lumbar spine (L2-L4), and total body; total body mineral content; serum osteocalcin and intact PTH.	295 healthy, elderly men and women (aged at least 68 years). All subjects were participants of a previous 3 year trial.	2 years	Subjects did not receive any treatment during follow-up study and were asked to avoid taking supplements. Subjects were participants of a previous randomized, placebo controlled 3 year trial involving treatment with calcium and vitamin D supplements against a placebo control.	Habitual diet			In 128 men, previous supplement-induced increases in spinal and femoral neck BMD were lost within 2 year of supplement discontinuation, but small benefit in total body BMD ($1.18 \pm 0.33g$, $p = 0.005$) was observed. In 167 women, there were no significant lasting effects in total body BMD or any other bone site. Bone turnover rates in both men and women as determined by osteocalcin concentrations returned to their original higher concentrations within the same 2 year period.	The authors conclude that discontinued calcium and vitamin D supplementation has a limited cumulative effect on bone mass in men and women aged at least 68 years.

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Dibba, B <i>et al.</i> Effect of calcium supplementation on bone mineral accretion in Gambian children accustomed to a low-calcium diet. <i>Am. J. Clin. Nutr.</i> 2000; 71:544	Randomized, double-blind placebo-controlled trial Measured: BMC, bone width, and BMD at the midshaft and distal radius of the left arm; midshaft radius of the ulna; dietary calcium intake by direct-weighting method over 2 days; plasma osteocalcin	160 healthy children (80 boys, 80 girls) aged between 8.3 and 11.9 years. Subjects medical history was free of any condition known to affect calcium or bone metabolism	12 months	<u>Control:</u> placebo tablets of similar shape, taste, and texture <u>Treatment:</u> 2 chewable calcium carbonate tablets (calcichew; Shire pharmaceuticals LTD and Nycomed Pharma AS) containing 500mg elemental calcium per tablet 5 days a week for 12 months.	Habitual diet Dietary Calcium Intake mean 338±142mg/d (not significantly different between control and treatment groups)		2 girls started menstruating during the intervention. The number of children who entered puberty at the start of the study or Tanner stage 2 - 5 or during the intervention did not significantly differ between control or experimental treatment groups.	Gains were greater in BMC and BMD at both the midshaft and distal radius in the experimental treatment group. Midshaft radius BMC (0.493±0.078g/cm, p = 0.034) BMD (0.498±0.05 g/cm ² , p ≤ 0.0001) Distal radius BMC (0.487±0.132 g/cm, p ≤ 0.0001) BMD (0.253±0.05 g/cm ² , p ≤ 0.0001) Calcium treatment group had significantly low osteocalcin levels (17.9±7.3 µg/L, p ≤ 0.0001) Supplementation of calcium had no significant effect on height, weight, or bone width at the midshaft or distal radius.	The authors conclude that calcium intake resulted in increased bone mineral status, possibly associated with decreased remodeling space. The authors further argue that continuing studies are needed for long-term benefits in these children.

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Hunter, D <i>et al.</i> A randomized controlled trial of vitamin D supplementation on preventing postmenopausal bone loss and modifying bone metabolism using identical twin pairs. <i>J. Bone Miner. Res.</i> 2000; 15:11	Randomized, placebo-controlled trial Measured: DPD, osteocalcin, BSAP, PTH, and 25-hydroxyvitamin D at baseline, 3, and 6 months; 25-hydroxyvitamin D at 24 months; VDR genotyping; BMD of lumbar spine (L1-L4), total hip, femur neck, forearm, and whole body; heel ultrasound	79 monozygotic postmenopausal twin pairs from the St. Thomas' U.K. Adult twin registry. Exclusion criteria: history of serious medical illness, participation in HRT, currently taking medications or dietary supplements known to affect bone metabolism	24 months	<u>Control:</u> (N=79) placebo tablet identical in appearance to treatment tablet <u>Treatment:</u> (N=79) 800 IU Vitamin D (1 400 IU tablet twice daily)	Habitual diet Mean daily calcium intake between 1000-1500 mg		5 identical twin pairs excluded at baseline due to very low BMD (N=4) and breast cancer diagnosis (N=1). 10 additional pairs were also excluded due to poor (< 80%) compliance (N=6) or study drop out (N=4).	No significant differences between control and treatment groups in serum biochemical measurements except for Vitamin D (6 months post treatment, $p < 0.001$) No significant treatment effect was observed at 24 months on BMD or calcaneal ultrasound change within twin pairs. Treatment response by VDR genotype revealed no significant differences in BMD. No significant change in serum PTH	The authors conclude that vitamin D supplementation, on its own, can not be recommended as an osteoporosis prevention for healthy postmenopausal women with normal vitamin D levels under the age of 70 years.

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Iwamoto, J. <i>et al.</i> . Effect of combined administration of vitamin D ₃ and vitamin K ₂ on bone mineral density of the lumbar spine in postmenopausal women with osteoporosis. <i>J. Orthop. Sci.</i> 2000; 5: 546.	Randomized intervention. Measured: BMD of the lumbar spine in the anteroposterior view by DXA.	N=92 osteoporotic women who were more than 5 years after menopause, aged 55-81 years. All subjects were part of a larger group of 187 women who were diagnosed with osteoporosis between July 1993 and April 1998 and since had randomly received some therapeutic intervention, such as vitamin D ₃ , vitamin K ₂ , calcitonin, etidronate, and/or calcium administration, and/or exercise. None of the subjects had a history of hormone replacement therapy or had taken medications known to affect bone metabolism. Nor had any subjects engaged in sporting activity for at least the most recent 5 years before the trial.	24 months	Four groups: vitamin D ₃ (1 α hydroxy vitamin D ₃ , 0.75 mg/day) administration (D group; n=29), vitamin K ₂ (menatetrenone, 45 mg/day) administration (K group; n=22), vitamin D ₃ plus vitamin K ₂ administration (DK group; n=21), and calcium (calcium lactate, 2 g/day) administration (C group; n=20).	Habitual diet. Seven day food records were completed during screening after which subjects were encouraged to have 1000 mg of calcium and 400 IU of vitamin D daily through food. At baseline the average calcium intake for the D, K, DK, and C groups were 505, 495.1, 476.6, and 495.3 mg/d, respectively.			In the C group, significant ($p < 0.001$) mean percent changes of -0.53% and -0.79% were measured at 1 and 2 years respectively when compared to baseline measurements. The corresponding changes were -0.44% and +0.38% in the D group, and -0.20% and +0.90% in the K group, and the changes at 2 years in both of these groups were significant ($p < 0.05$) when compared to the C group. In the DK group, there was a change from baseline of +1.49% at 1 year this was significant when compared to the C, D, and K groups ($p < 0.01$, $p < 0.01$, $p < 0.05$, respectively). At year 2 the change was +1.35% which was significantly different from the C group ($p < 0.01$).	The authors conclude that combined administration of vitamin D ₃ and vitamin K ₂ compared with calcium administration, appears to be useful in increasing the BMD of the lumbar spine in postmenopausal women with osteoporosis.

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Merrilees, M et. al. Effects of dairy food supplements on bone mineral density in teenage girls. Eur J Nutr 2000; 39:256	Randomized controlled study Measured: Bone mineral density (hip spine, and total body), body composition, lipids profile, hydroxyproline excretion, urinary calcium and sodium excretion.	N=91 teenage girls post puberty n=205 girls between 15-16 completed questionnaire n=184 recruited but only n=105 met inclusion criteria and volunteered. Exclusion: thyroid disorders, renal impairment, hepatic dysfunction, pregnancy, oligomenorrhoea, amenorrhoea, current systemic illness, eating disorders, anorexia, use of glucocorticoids, anticonvulsant agents or thiazide diuretics.	2 years, 1 year follow-up	All examined at beginning of study and every 6 months for 2 years, then there was a 1 year follow-up. Control group: normal diet Supplemental group: Dairy foods to at least 1000 mg / d, delivered fortnightly. Girls were allowed to self select (with help of dietitian) what they ate from a variety of choices to equal 1000 mg per day. Girls were randomly placed into groups using forearm BMD at baseline for stratification	Habitual diet		N=91 completed the first 2 years N=14 moved out of study area, n=3 developed eczema or migraines, n=1 failed to comply, n=4 moved out of study area in control. Only n=73 girls available for 1 year follow-up (due to moving, unable to contact, and did not want to participate). This study used dairy products as a source of calcium. Therefore it is not possible to conclude that the positive effects on bone was due to calcium or some other component in milk. Nevertheless, it provides suggestive evidence that dietary calcium is beneficial to bone quality.	Supplemental group was significantly higher in calcium, phosphorus and protein intake ($p<0.001$). No difference between groups after 12 months post supplement. No significant difference in lipids and bone markers between baseline and end of supplement and 1 year follow-up. There was a significant increase in trochanter (4.6%), lumbar spine (1.5%) and femoral neck (4.8%) BMD ($p<0.05$) in the high calcium group. There was an increase in bone mineral content at trochanter ($p<0.05$) and lumbar spine in the high Ca group but the lumbar spine was not significant. No difference in vertebral height or width which indicates no influence on bone size. Ca intake in control group at 0, 2 years and follow-up were 765.3, 683.9, and 651.6 mg/d respectively. In the supplemental group they were 744.1, 1155.1, & 695 mg/d.	The authors conclude that teenage girls aged 15-18 years can significantly increase their BMD at the trochanter, femoral neck, and lumbar spine with dairy supplementation to a mean calcium intake of 1160 mg / d. After 12 months of study the girls returned to a normal diet indicating self-selection of high dairy products in the diet is hard to achieve.

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Peacock, M et al.. Effect of calcium or 25OH Vitamin D ₃ dietary supplementation on bone loss at the hip in men and women over the age of 60. The Journal of Clinical Endocrinology and Metabolism. 2000; 85:3011.	Randomized, placebo-controlled, double blind trial. Measured: BMD, bone structure, calcium biochemistry and bone turnover markers measured in blood and urine, fracture history.	N=316 women (mean age 73.7) N=122 men (mean age 75.9) Recruited via advertisements and organizations for retirees from 2 retirement homes and surrounding neighborhoods. Over 60% were free living. All were independently mobile. All able to give consent. Exclusion: terminal illness; pagets disease of bone; recurrent urinary stone disease; treated with sodium fluoride, bisphosphonate, steroids, or dilantin; renal disease requiring specific treatment; or excluded by their primary physician. Low BMD, previous skeletal fractures and ERT were not exclusions.	4 years	Subjects randomized to 1 of 16 strata by age (60-74 and ≥75), sex, serum 25OH vitamin D concentration (< 60nmol/l and ≥60nmol/l) and dietary calcium intake (<480 mg/d and ≥480 mg/d) after baseline studies. 3 groups: 1) n=124; 250 mg Ca 2) n=124; 5 µg 25OH vitamin D ₃ 3) n=129; placebo Supplements were taken 3 times a day with meals	Median calcium intake was 546 mg/d Median 25OH vitamin D ₃ was 59 nmol/l		Compliance was 80% (SD=20%) for Ca group, 89% (SD=16%) for 25OH vitamin D ₃ group, and 85%(SD=19%) for placebo.	Placebo: loss of BMD at total hip was 2%, femoral medulla expansion was 3% over 4 years. Placebo group lost BMD at total hip, Ca group did not, loss of BMD in 25OH vitamin D ₃ group intermediate (overall treatment effect was significant (p=0.017). Change in BMD at total hip in Ca group was significantly different from the placebo (p<0.008) but not from the 25OH vitamin D ₃ group.	The authors conclude that calcium supplementation of 750 mg/d prevents loss of BMD, reduces femoral medullary expansion, secondary hyperparathyroidism and high bone turnover. 15µg/d 25OH vitamin D ₃ effects seen only at low calcium intake which suggests it is beneficial to reverse calcium insufficiency.

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Sosa, M et. al.. The effect of 25-dihydroxyvitamin D on the bone mineral metabolism of elderly women with hip fracture. Rheumatology. 2000;39:1263.	Open, prospective study with a 1 year follow-up Measured: biochemical markers of bone remodeling, serum calcium, and parathyroid hormone, bone mineral density in lumbar spine and proximal femur, and serum osteocalcin.	N=70 women Inclusion: Suffered fracture of proximal femur between May 1994 and Dec. 1997, able to walk. Exclusion: confined to bed	Treatment time not mentioned 1 year follow-up	N=28 25-HCC group: 1 g/d calcium orally (divided into 2 doses) + 1 ampoule of 25-hydroxycholecalciferol (Hidroferol) which contains a dose of 0.622 mg (10640IU)/wk. N=30 control group: 1 g/d calcium orally (divided into 2 doses)	Current calcium intake estimated from 24 hour checklist survey Habitual diet Baseline calcium intake mg/d: 25-HCC 667 ±446 control 654±318		N=58 completed the study N=12 excluded for non-compliance with treatment, starting other therapy which would influence bone mineral metabolism, readmission to a hospital, or leaving the study. N=7 in 25-HCC group left study N=5 in control group left study	After 1 year of treatment 25-HCC corrected secondary hyperparathyroidism, increased urine calcium excretion, increased bone mass in the femoral neck, but there was no effect on appearance of new fractures. In the femoral neck, an increase of 2.1% was observed in bone density in the 25-HCC and the calcium group whereas patients treated only with calcium showed a loss of 1.8% (p<0.05).	The authors conclude that daily treatment with 1 g calcium + 25-HCC (0.260 mg/wk) reduces previously high serum levels of PTH without modifying calcaemia and increases calcuria and bone mineral density in the femoral neck of elderly women who have suffered FPF. It does not change biochemical markers of bone remodeling or in bone mineral density of the lumbar spine and does not decrease the rate of appearance of new fractures. The authors conclude that this intervention would not be able to reduce fractures in an at-risk population.

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Bonjour, J P et. al.. Gain in bone mineral mass in prepubertal girls 3-5 years after discontinuation of calcium supplementation: a follow-up study. The Lancet. 2001; 358:1208.	Follow-up to previous intervention (randomized, double blind placebo controlled) Measured: areal bone mineral density (distal metaphysis of the radius, diaphysis of the radius, femoral neck, femoral trochanter, mid femoral diaphysis, and L2-L4 vertebrae in anteroposterior view).	Healthy prepubertal white girls, mean 7.93 years Exclusion: no parental approval, wt/ht ratio lower than the third or greater than the 97 th percentile, signs of puberty, chronic disease, gastrointestinal disease capable of inducing malabsorption, congenital or acquired bone disease, regular use of medication. N=149	48 weeks	Calcium enriched foods group: n=65; two supplements/d for average of 850 mg Ca (calcium phosphate extract from milk used to enrich cakes, biscuit, fruit juices, powdered drinking chocolate, chocolate bars and yogurt) Placebo group: n=54 similar food products with respect to energy, protein, lipid and mineral content but with the added supplement that is in the calcium group New measurements taken 3.5 years post treatment	Estimate of Ca intake obtained by frequency questionnaires at baseline, 24 weeks, 48 weeks, and 3.5 years post intervention		N=144 with mean age of 12.5 years completed study	There was an increase from baseline in overall mean bone mineral density of 6 skeletal sites that was significant (Ca-supplemented 179 mg/cm ² [SE8] vs. placebo group 151 mg/cm ² [SE7], p=0.012). There was a significant difference in favor of the supplemental Ca group seen with respect to the mean bone mineral content (p=0.031) and mean bone area (p=0.04). There was a difference in pubertal maturation that did not account for the recorded differences. The mean spontaneous Ca intake at the end of the intervention was 917 mg/d (SE47) in the Ca group and 955 mg/d (SE 47) in the placebo group. At follow-up the Ca group was 880 mg/d (SE 46) and the placebo group was 920 mg/d (SE49). So spontaneous Ca intake remained constant and did not differ significantly between groups.	The authors conclude that the form of milk extracted Ca phosphate taken during the prepubertal period can modify the trajectory of bone mass growth and cause a long lasting increase in bone mass accrual beyond the end of supplementation.

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Patel, R et. al.. The effect of season and vitamin D supplementation on bone mineral density in healthy women: a double masked crossover study. Osteoporos Int. 2001; 12:319.	Double-masked, placebo controlled, randomized crossover study Measured: lumbar spine, left proximal femur, total body BMD (at 3 month intervals); serum 25-hydroxyvitamin D (25-OHD), serum PTH, bone markers and urinary crosslink's and Ca absorption.	N=70 healthy female volunteers with a mean age of 47.2 years Inclusion: hospital staff, patients referred for bone densitometry investigations by primary physicians Exclusion: treatment for osteoporosis (estrogen, etidronate, alendronate, calcitonin, fluoride or Ca or vitamin D supplements) N=39 subjects were premenopausal N=31 were postmenopausal	2 years	First year: Group 1 N=35 800IU (20µg) cholecalciferol per day Group 2 N=35 placebo Second year: Reverse of what they received the first year	A questionnaire was given that included daily Ca intake from dairy products The mean Ca intake for group 1 was 553 mg (SD 207), group 2 was 586 (SD 224) The mean 25-OH vitamin D (nmol/l) for group 1 was 68.1 (SD 20.3) and for group 2 75.7 (SD 19.0)		N=20 from the treatment group and n=23 from the placebo group completed the full 2 years	Cholecalciferol increased serum 25-OHD by 25.4 nmol/l ($p<0.001$), while a reciprocal decrease in serum PTH of 6.6 ng/l ($p=0.011$) was seen in subjects in the lowest quartile of baseline serum 25-OHD. There was no significant effect on spine, femur or total body BMD calcium absorption on bone markers with treatment. There was a highly significant effect for 25-OHD of 18nmol/l ($p<0.001$) when analyzed for seasonal effect. There was no effect for BMD, PTH, Ca absorption on bone markers	The authors concluded that in the population of healthy women studied there was no evidence of seasonal variation in spine, femur or total body BMD, serum PTH, Ca absorption or bone markers. They found that vitamin D supplementation had no effect on BMD.

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Shapses, S A et. al.. Bone turnover and density in obese premenopausal women during moderate weight loss and calcium supplementation. Journal of Bone and Mineral Research. 2001; 16:1329.	Randomized double-blind study Measured: total body and lumbar spine, (determined changes in BMD, BMC, and total body fat mass (FM) and lean mass (LM)), serum osecalcin, serum parathyroid hormone, serum 25-hydroxyvitamin D	N=60 obese postmenopausal women age 42.1±6.2 years. BMI 34.0±3.9 kg/m ² All had to be weight stable for at least 3 months prior to start of study Inclusion: Women who had not been pregnant or lactating within the previous year and had a history of regular menstrual cycle. Exclusion: Ill or taking medications known to interfere with bone metabolism (oral contraceptives included) All had regular menstrual cycles throughout the study	6 months	N=14 Ca supplemented (all white) 1000mg elemental Ca (calcium citrate) N=14 placebo (9 white, 3 black, 1 Asian, 1 Hispanic) placebo tablets N=19 weight maintenance (9 white, 1 Hispanic) Doses given at breakfast and dinner At completion the placebo group was divided into those that did and did not lose > 2.5% of initial body weight. Those that did not lose were included in a 2 nd control group that included women recruited to maintain body weight.	Habitual diet Their usual calorie and nutrient intake were determined based on food frequency and 24 hr diet recalls. A reduced calorie diet was individually created using the American diabetic association exchange list. Subjects were encouraged to keep a diary of daily diet recalls, physical activity and menstrual cycles.		N=22 dropouts N=38 completed the study (37% dropped out) Dropouts because of lack of commitment to weight loss program because of personal reasons, dramatic increase in physical activity, failed to lose enough weight, degree of compliance with Ca supplements (determined by pill counts)	Calcium intakes at baseline and after weight loss for the Ca supplement group were 1005 ±390, 1835±235, the placebo group were 810±335, 459±145, and for the wt. maintenance group 1152±367, and 795±244, respectively. Vitamin D intakes were as follows at baseline and after wt. Loss: For the Ca supplemented group, 2.8±2.4, 2.1±1.4, for the placebo group 2.0±1.1, 1.5±0.9, and for the wt. maintenance group 2.0±1.4, and 2.7±2.2. In moderate energy restriction, dietary Ca intake decreased (p<0.05) and bone resorption marker deoxypyridinoline (DPD) increased slightly (p<0.05) without evidence of bone loss. Calcium supplementation during weight loss tended to increase lumbar BMD by 1.7% (p=0.05) compared with the placebo or weight maintenance groups.	The authors conclude that premenopausal obese women who consume a low Ca diet do not lose bone over a 6 month period whether their weight is stable or decreasing moderately.

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Heaney RP <i>et al.</i> Effect of yogurt on a urinary marker of bone resorption in postmenopausal women. <i>J. Am. Diet. Assoc.</i> 2002;102:11	Randomized, cross-over study. Measured: urinary N-telopeptide cross-links (NTx), creatinine, and calcium; dietary nutritional content by diet diary.	(N=29) white postmenopausal women aged 61±4.3 years with a BMI of 27.3±3.9 kg/m ² . Exclusion criteria: Estrogen replacement therapy, calcium supplementation, dietary calcium intakes greater than 600 mg/day.	6 weeks	<u>Cross-over protocol</u> : All subjects (N=29) were randomly assigned to eat both a non-nutritious jelled fruit-flavored snack and fruit-flavored yogurt (Yoplait custard style, General Mills) on a cross-over basis three times a day between midday and bedtime for a period of 7 to 11 days. Followed by a two-week washout period before switching over to the opposing snack for an additional 7 to 11 days.	Habitual diet. No other restrictions were made with respect to food consumption or dietary instruction. Baseline mean dietary calcium intake was 466±105 mg/day.		At baseline, 3 of 29 subjects had diets below the cutoff (70% recommend intake) for protein. Many of the women had diets low in magnesium and zinc under all three conditions (jelled snack, yogurt, and baseline).	Urinary calcium increased significantly under the yogurt treatment (P<0.03). Urinary NTx decreased significantly under the yogurt treatment to 22% lower than their jelled snack counterpart (P<0.03). Diet quality improved on the yogurt and deteriorated on the jelled snack diet.	The authors conclude that diets low in dairy intake are often marginal for several nutrients and that, as far as calcium is concerned, bone makes up for what diet lacks. The authors further conclude that bone resorption responds rapidly and sensitively to improvements in calcium intake that are readily achievable by an older female population.

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Jensen, C et. al.. Long-term effects of nutrient intervention on markers of bone remodeling and calciotropic hormones in late-postmenopausal women. Am J Clin Nutr 2002; 75:1114.	Randomized double blind for treatments, not for dietary control Measured: calcium intakes, serum 25-hydroxyvitamin D, parathyroid hormone	N=99 healthy postmenopausal (for ≥ 5 years) women with an average age of 66 ± 5 years Asked to discontinue non study dietary supplements 30 days before baseline, maintain usual physical activity and report medications changes. Exclusions: current or recent use (past 6 months) of hormone replacement medication, thiazide diuretics, or glucocorticoids and the presence of chronic illnesses (diabetes, kidney disease, heart disease cancer or known parathyroid disease).	3 years	1) n=26 supplemental Ca (1450 mg/d) + Vitamin D [$10\mu\text{g}(400\text{IU})/\text{d}$] 6 tablets per day as a supplement + 850 mg P 2) n=32 calcium + vitamin D + multinutrient supplement. 6 tablets/d of supplement 1450 mg Ca/d, 850 mg P, 10 μg (400IU) vitamin D, and a multinutrient supplement. 3) n=25 dietary instruction or dietary control group. Consumption of ≥ 800 mg Ca/d with ideal goal of 1450 mg/d	Habitual diet. Daily Ca consumption of 793 ± 280 mg		A true placebo was not used because of ethical considerations posed by the length of the study and the potential for significant bone loss in women with inadequate dietary Ca and vitamin D intakes. N=83 completed the total 3 years N=16 withdrew because of difficulty maintaining the diet, side effects of supplements, difficulty swallowing tablets, supplement intolerance, indigestion, constipation, night sweats, and hot flashes.	There were increases over baseline in Ca intakes and serum 25-hydroxyvitamin D concentrations sustained over 3 years in all treatment groups. There was reduced circulating parathyroid hormone concentrations after 1 year in all treatment groups but tended towards baseline thereafter. Bone turnover markers followed a similar pattern and none of the changes in biochemical concentrations differed significantly between groups. The Ca intakes for baseline and the end of the study are as follows for each group: dietary control, 871 ± 373 mg/d, 1122-1242, for Ca + vitamin D 672 ± 158 , 2122-2178, for multinutrient, 831 ± 246 , and 2246-2345 respectively. The vitamin D intakes for baseline and end of study were as follows: For dietary control, $3.45 \pm 3.9\mu\text{g}/\text{d}$, 4.33-6.03, for Ca + Vitamin D 4.45 ± 8.03 , 2.85-9.83, and for multinutrient group 3.95 ± 7.3 , and 3.3-8.90, respectively.	The authors conclude that the addition of micronutrients had no obvious bone sparing effect in healthy postmenopausal women beyond that of Ca and vitamin D alone. All 3 interventions were effective in increasing Ca intake and serum 25-hydroxyvitamin D concentrations.

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<p>Meyer, H E, <i>et al.</i> Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. <i>J Bone Miner Res.</i> 2002; 17: 709.</p>	<p>Randomized control trial, double-blind</p> <p>Measured: hip fractures; 25-hydroxyvitamin D, serum PTH, osteocalcin, ionized Ca</p>	<p>Nursing home residents in 2 Norwegian cities.</p> <p>N=1144 residents (including mentally impaired persons) mean age of 84.7 years. 75% were women.</p> <p>Inclusion: Life expectancy of more than ½ a year; not to be permanently bedridden; no difficulties taking medications (those already taking vitamin D supplement as long as they did not exceed 10µg / d were included).</p>	<p>3 years</p>	<p>Randomly assigned based on day of birth.</p> <p>Control group: n=575 5 ml cod liver oil/d with vitamin D removed</p> <p>Intervention group: N=569 5 ml cod liver oil/d</p> <p>supplements were delivered by the nursing staff along with patients other medications each day.</p>	<p>Questionnaire filled in by nursing staff at baseline (included Ca intake, height, weight, previous hip fracture, falls in the last 3 months, and mobility status).</p> <p>Habitual diet based on what was offered at the nursing home.</p>		<p>N=383 received cod liver oil treatment throughout the study.</p> <p>N=332 discontinued treatment because of death.</p> <p>N=429 stopped treatment for other reasons.</p>	<p>N=47 in the control group and n=50 in the vitamin D group suffered a hip fracture. N=76 in the control and n=69 in the vitamin D group suffered non vertebral fractures. There was no difference in incidence of hip fractures (p=0.66 log-rank test) or in the incidence of all nonvertebral fractures (p=0.60, log-rank test) in the vitamin D group compared with the control group. Persons in the vitamin D group increased serum 25-hydroxyvitamin D concentrations with 22nmol/l (p<0.001) compared with the control groups. There was no statistical difference between groups concerning change in serum PTH, serum ionized Ca, or serum osteocalcin.</p>	<p>The authors conclude that an intervention with 10µg of vitamin D₃ alone produce no fracture-preventing effect in a nursing home population of frail elderly people.</p>

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Ushiroyamon, T et al. Effect of continuous combined therapy with vitamin K ₂ and vitamin D ₃ on bone mineral density and congulofibrinolysis function in postmenopausal women. Maturitas. 2002; 41: 211.	Controlled, randomized intervention. Measured: Vertebral BMD by dual-energy x-ray absorptometry (DEXA). Bone metabolism markers were analyzed and tests of blood coagulation performed.	N=172 Postmenopausal women (mean age of four groups ranged from 52.8 to 54.1 years of age) with vertebral bone mineral density <0.98 g/cm ² . Subjects with BMD values below 0.98 g/cm ² were considered to have osteopenia and those with BMDs below 0.83 g/cm ² were considered to have osteoporosis.	24 months	Four groups: vitamin K ₂ therapy group (n=43; menaquinone-4 Glakay 45 mg/day), vitamin D ₃ therapy group (n=43; 1-α-hydroxycholecalciferol: Oneulfa 1 μg/day), vitamin K ₂ and vitamin D ₃ combined therapy group (n=43), and control group receiving diet alone.	Habitual diet. Patients were given specific instructions regarding adequate dietary calcium intake and did not take part in a program of exercise.		46 out of 172 subjects failed to complete the study. Many of the dropout patients had high BMD. This was particularly true in the combined therapy group and the remaining patients in this group had a basal level of BMD that was significantly lower than these in the vitamin K ₂ or D ₃ alone therapy group. This appears to have biased the data.	Combined vitamin K ₂ and D ₃ treatment for 24 months significantly increased BMD 4.92% (p<0.001) over baseline while vitamin K ₂ alone only BMD 0.135% (p<0.05). Compared with the vitamin K ₂ or D ₃ alone therapy group, BMD was significantly increased in the combined therapy group from 6 to 24 months after the start of treatment (vitamin D ₃ -combined therapy; p<0.001, vitamin K ₂ -combined therapy; 0<0.01). An increase in coagulation and fibrinolytic activity that was within the normal range was observed, suggesting that balance was maintained in the fibrinolysis-coagulation system.	The authors conclude that the continuous combination therapy with vitamin K ₂ and D ₃ may be useful for increasing vertebral bone mass in postmenopausal women.

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Bischoff, H A, et al. Effects of vitamin D calcium supplementation on falls: a randomized controlled trial. J Bone Miner Res. 2003; 18: 343.	<p>Double-blind, controlled, randomized intervention.</p> <p>Measured: Number of falls per person; 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D serum levels; change in musculoskeletal function (summed score of knee flexor and extensor strength, grip strength, and the timed up and go test) was a secondary measurement.</p>	<p>N=122 Elderly women (mean age, 85.3 years; range, 63-99 years) in long-stay geriatric care.</p> <p>Patients had to be age 60 or older and had to be able to walk 3m with or without walking aid.</p> <p>Exclusion criteria included primary hyperparathyroidism, hypocalcemia, hypercalciuria, renal insufficiency (creatinine >117 μM), and fracture or stroke within the last 3 months. Also excluded were those who had received any treatment with hormone replacement therapy, calcitonin, fluoride, or bisphosphates during the previous 24 months.</p>	6-week pretreatment period and 3 months treatment period	<p>Vitamin D and Calcium group (Cal + D group, n=62) received two tablets containing 600 mg of calcium carbonate and 400 IU of cholecalciferol per tablet.</p> <p>Calcium group (Cal-group, n=60) received two tablets containing 600 mg calcium carbonate per tablet.</p> <p>Tablets were administered twice per day with breakfast and dinner.</p>	<p>Habitual diet.</p> <p>A dietitian evaluated the mean calcium content of food consumed from each meal and drink during the baseline week.</p>			<p>Among subjects in the Cal+D group, there were significant increases in median serum 25-hydroxyvitamin D (+71%) and 1,25 dihydroxyvitamin D (+8%).</p> <p>Cal+D-treatment accounted for a 49% reduction of falls (95% CI, 14-71%; p< 0.01) based on fall categories: number of falls per person (0,1,2-5,6-7,>7).</p> <p>Among fallers in the treatment period, the crude average number of excessive falls was significantly higher in the Cal-group (p=0.045).</p> <p>Musculoskeletal function improved significantly higher in the Cal+D-group (p=0.0094).</p>	<p>The authors concluded that a single intervention with vitamin D plus calcium over a 3-month period reduced the risk of falling by 49% compared with calcium alone.</p> <p>Recurrent fallers seem to benefit most by the treatment.</p> <p>The authors concluded that the impact of vitamin D on falls might be explained by the observed improvement in musculoskeletal function.</p>

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Couley, J A, <i>et al.</i> Effects of estrogen plus progestin on risk of fracture and bone mineral density. The women's health initiative randomized trial. JAMA. 2003; 290: 1729.	Randomized controlled trial. Measured: All confirmed osteoporotic fracture events that occurred from enrollment to discontinuation of the trial (July 7, 2002); BMD in a subset of women (n=1024) at baseline and years 1 and 3; and a global index developed to summarize the balance of risks and benefits to test whether the risk-benefit profile differed across tertiles of fracture risk.	N=16,608 postmenopausal women with intact uterus who were aged 50 to 79 years at baseline.	Variable: average follow-up of 5.2 years. For subjects used for BMD measurement, duration was 3 years.	Conjugated equine estrogen 0.625 mg/ day plus medroxyprogesterone acetate, 2.5 mg/ day, in 1 tablet (n=8506). Placebo group (n=8102).	Habitual diet.		Included in estrogen+progestin group 296 had unknown vital status and 248 were deceased on July 7, 2002. Included in placebo group 245 had unknown vital status and 237 were deceased on July 7, 2002.	Seven hundred thirty-three women (8.6%) in the estrogen-plus-progestin group and 896 women (11.1%) in the placebo group experienced a fracture (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.69-0.83). Total hip BMD increased 3.7% after 3 years of treatment with estrogen plus progestin compared with 0.14% in the placebo group (p<0.001). The HR for the global index was similar across tertiles of the fracture risk scale (lowest fracture risk tertile, HR, 1.20; 95% CI, 0.93-1.58; middle tertile, HR, 1.23; 95% CI, 1.04-1.46; highest tertile, HR, 1.03; 95% CI, 0.88-1.24) (p for interaction = .54).	The authors conclude that estrogen plus progestin increases BMD and reduces the risk of fracture in healthy postmenopausal women. The decreased risk of fracture attributed to estrogen plus progestin appeared to be present in all subgroups of women examined. The authors state that when considering the effects of hormone therapy on other important disease outcomes in a global/model, there was no net benefit, even in women considered to be at high risk of fracture.

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Chee, W S S, <i>et al.</i> The effect of milk supplementation on bone mineral density in postmenopausal Chinese women in Malaysia. <i>Osteoporosis Int.</i> 2003; 14: 828.	Controlled randomized intervention. Measured: Lumbar spine, femoral neck, total hip, and total body BMD by DXA; serum PTH and 25-(OH) D.	N=200 Chinese women 50 to 60 years old and more than 5 years postmenopausal. Subjects were excluded if they had a history of bone disease or medical conditions that affect bone metabolism (e.g. hormone/ estrogen replacement therapy, thiazide diuretics, glucocorticoids) or had other chronic illnesses (such as diabetes, kidney disease, heart disease, or cancer). Women taking calcium supplementation (>500 mg/ day) for longer than a month or were already drinking 2 or more glasses of milk a day were also excluded.	24 months	Intervention group (n=91) received 50g of high-calcium skimmed milk powder (Anlene Gold™, New Zealand Milk) which continued 1200mg calcium (taken as two glasses of milk a day). Control group (n=82) continued with their usual diet.	Habitual diet. Baseline calcium intake was 470 mg/ day in the treatment group and 466 mg/ day in the placebo group (from 3-day food records).		27 subjects out of 200 failed to complete the study (n=18 milk group, n=9 in placebo). The milk group had lower baseline BMD at the total body (p< 0.01), femoral neck (p< 0.001), and total hip (p< 0.001) compared to the control group, though the absolute differences were small. These differences, however, were controlled as covariates when comparing percentage changes in BMD between groups.	Milk supplement significantly reduced the percentage of bone loss at the total body at 24 months (control - 1.04%, milk -0.13%; p< 0.001). Similarly, milk supplementation reduced percentage of bone loss at the lumbar spine (control -0.90%, milk -0.13%, p< 0.05), femoral neck (control - 0.1.21%, milk -0.51%, p< 0.01), and total hip (control -2.17%, milk - 0.50%, p<0.01). Serum 25-(OH) D improved significantly (p< 0.01) from 69.1± 16.1 nmol/l at baseline to 86.4± 22 nmol/l at 24 months in the milk group. Control subjects had significantly higher levels of PTH from baseline (p< 0.05) and from the milk group (p< 0.05) at 24 months.	The authors conclude that ingestion of high calcium skimmed milk was effective in reducing the rate of bone loss at clinically important spine and hip sites in postmenopausal Chinese women in Malaysia.

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Grados, F et. al.. Effects on bone mineral density of calcium and vitamin D supplementation in elderly women with vitamin D deficiency. Joint Bone Spine 2003; 70:203.	Randomized, double-blind, placebo-controlled study Measured: Lumbar spine, femoral neck, trochanter, and whole body BMD by DXA, serum PTHi and 25-(OH)D	N=192 women (mean age 75±7 years) with vitamin D deficiency, defined as serum 25(OH)D concentration ≤12ng/ml. Patients were recruited at 10 centers distributed throughout France. Additional inclusion criteria were a serum creatinine level lower than 130 µmol/l and a serum calcium level lower than 2.62 mmol/l.	12 months	Calcium-vitamin D group (n=95) received 500 mg/d of elemental calcium as calcium carbonate and 400 IU of vitamin D (ID EOS® tablets) Placebo group (n=97)	Habitual diet Baseline daily calcium intake 697 mg/d in Ca-Vitamin D and 671 mg/d in placebo. (estimated using FFQ) Baseline vitamin D intake 67 IU/d in Ca-Vitamin D and 62 IU/d in placebo. (estimated using FFQ)		61 subjects out of 192 failed to complete the study	The median in serum 25-(OH)D was 22ng/ml in the supplemented group and 4 ng/ml in the placebo group(p<0.0001), and the median PTHi decrease was 17 and 5 pg/ml, respectively (p<0.0001). The median BMD increase was significantly greater in the supplemented group than in the placebo group: +2.98% vs. -0.21% at lumbar spine (p=0.0009), +1.19% and -0.83% at the femoral neck (p=0.015), +0.86% and -0.58% at the trochanter (p=0.015) and +0.99% and +0.11% for the whole body (p=0.01).	The authors conclude that bone mass in older women with vitamin D deficiency increases significantly at the lumbar spine, femur, trochanter, and whole body after calcium and vitamin D supplementation for 1 year, and concomitantly bone markers improved as vitamin D levels returned to normal.

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Rozen, G S, et. al.. Calcium supplementation provides an extended window of opportunity for bone mass accretion after menarche. Am J Clin Nutr 2003; 78:993.	Double-blinded, placebo-controlled, randomized intervention Measured: BMD (by DXA) and bone mineral content (BMC) of the total body, lumbar spine, and femoral neck; serum PTH.	N=112 girls (mean age 14 years) with an ethnic distribution of 85 Jewish girls and 27 Arab girls. Inclusion criteria included calcium intake <800 mg/d, ≥1 year postmenarchal age, age <15.5 years, no chronic disease, non smoking, and no use of contraceptives. All subjects were recruited from an earlier cross-sectional study of food habits and bone health among high school girls.	12 months	Calcium supplementation (CS) group (n=49) received 1000 mg elemental Calcium/d in the form of calcium carbonate chewable tablets. Control group (n=51) received identically shaped placebo tablets.	Habitual diet Calcium intake was 578.2 mg/d for the placebo group and 586.7 mg/d for the calcium-supplemented group. Calcium intake was determined by a trained dietitian.		12 subjects out of 112 failed to complete the study. Compliance dropped from 71 ± 26% during the initial 6 months to 56 ± 34% for the remaining study period (p=0.0001).	The accretion of total body BMD was higher in the CS group than in the control group (3.80% compared with 3.07%, p<0.05). The percentage accretion of BMD in the lumbar spine was higher in the CS group than in the placebo group (3.66% compared with 3.00%, p<0.05) and BMD in the femoral neck tended to be higher in the CS group though this was not significant. Serum PTH concentrations dropped significantly in the CS group after 6 months of treatment by 4.40 pg/ml, compared with an increase in the placebo group of 2.30 pg/ml. This difference was no longer significant after 12 months. There was a significant interaction between time since menarche and treatment group on total body mass accretion at the end of the survey period (p=0.014).	The authors conclude that calcium supplementation of postmenarchal girls with low calcium intakes enhances bone mineral acquisition, especially in girls > 2 years past the onset of menarche.

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<p>Trivedi, D P et. al.. Effect of four monthly oral vitamin D₃ (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial. BMJ, 2003; 326:469.</p>	<p>Randomized, double-blind, controlled trial.</p> <p>Measured: Fracture incidence and total mortality by cause.</p>	<p>N=2686 people (2037 men and 649 women) aged 65-85 years living in the general community, recruited from the British doctors register and a general practice register in Suffolk.</p> <p>Subjects were excluded if they were already taking vitamin D supplements and those with conditions that were contraindications to vitamin D supplementation for example, a history of renal stones, sarcoidosis or malignancy.</p>	<p>5 years</p>	<p>Treatment group (n=1345, 1019 men and 326 women) received one capsule containing 100,000IU vitamin D₃ (cholecalciferol) every four months for five years (15 doses total).</p> <p>Placebo group (n=1341, 1018 men and 323 women) received placebo tablets.</p>	<p>Habitual diet.</p>			<p>268 men and women had incident fractures, of whom 147 had fractures in common osteoporotic sites (hip, wrist or forearm, or vertebrae). Relative risks in the vitamin D group compared with the placebo group were 0.78 (95% CI 0.61 to 0.99, p=0.04) for any first fracture and 0.67 (0.48 to 0.93, p=0.02) for first hip, wrist or forearm, or vertebral fracture.</p> <p>471 participants died. The relative risk for total mortality in the vitamin D group compared with the placebo group was 0.88 (0.74 to 1.06, p=0.18).</p>	<p>The authors conclude that supplementation every four months with 100,000 IU oral vitamin D may prevent fractures without adverse effects in men and women living in the general community.</p>

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Stear, S J et. al.. Effect of a calcium and exercise intervention on the bone mineral status of 16-18 year old adolescent girls. Am J Clin Nutr 2003; 77:985.	Double-blind, placebo-controlled, randomized intervention. Measured: Bone mineral content (BMC) and bone area of the whole body, lumbar spine, nondominant forearm, and left hip were measured by DXA.	N=144 female students with a mean age of 17.3 years were recruited from the 2 main sixth-form colleges in Cambridge, United Kingdom and were on average 4.7 years postmenarche. Exclusions included any medical problem, a history of eating disorders; and medication use known to interfere with bone metabolism.	15.5 months	Calcium supplementation (n=65) received 2 tablets/d (chewable, orange-flavored calcium carbonate containing 500 mg Ca/tablet) one midmorning and one late in the afternoon for a total supplement of 1000 mg Ca/d. Placebo (n=66) received placebo tablets. Subjects in each group were randomly allocated to 1 of 2 exercise groups: group E (n=75) were invited and encouraged to attend three 45 min exercise to music classes a week; group N (n=56) were not invited to these sessions.	Habitual diet. Average baseline calcium intake for all subjects was 938 mg/d as estimated by a FFQ.		13 subjects out of 144 failed to complete the study. The mean percentage of subjects compliant with supplement taking was 70±27% and with exercise class attendance was 36±25%.	Calcium supplementation significantly increased size-adjusted bone mineral content. The percentage difference was greater in subjects with good compliance (>75% compliance): whole body 0.8% (p≤0.01); lumbar spine, 1.9% (p≤0.001); ultradistal radius, 1.3%(p≤0.05); total hip, 2.7% (p≤0.0001); femoral neck, 2.2%(p≤0.0001), trochanter, 4.8% (p≤0.0001). Attendance at > 50% of the exercise sessions was significant at the total hip (1.4, p≤0.05) and trochanter (2.6; p≤0.05).	The authors conclude that calcium supplementation and exercise enhanced bone mineral status in adolescent girls.

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Matkovic, V., <i>et al.</i> Nutrition influences skeletal development from childhood to adulthood: a study of hip, spine, and forearm in adolescent females. <i>J Nutr.</i> 2004; 134: 701S	Randomized, double-blind placebo controlled clinical trial Measured: Bone mineral areal density of the total body and forearm BMD by DXA; hip, and spine BMD by peripheral Quantitative Computed Tomography (pQCT); metacarpal radiogramme -try; nutritional status by 3-day dietary food records using Nutritionist III, v8.5	Two cohorts of healthy Caucasian young females (total number = 314) in pubertal stage two with an average chronological age at baseline = 10.8±0.8 years. Cohort one participated in the long-term clinical trial with calcium or placebo supplementation, while cohort two participated in the observational study with higher intake from dairy products. Exclusion criteria not stated	7 years	Cohort selection was determined by a calcium intake threshold of 1480 mg/day as determined by questionnaire. All subjects below the threshold were assigned to the clinical trial. Those subjects whose intake was above the threshold were assigned to the observational study. <u>Clinical trial</u> <u>Experimental group</u> (n=103) 1000mg/4 pills/day of Calcium Citrate Malate (CCM). 2 pills were taken <u>Control group</u> (n=123) received a placebo CCM supplements and placebo pills were supplied by Procter & Gamble. <u>Observational study</u> (N=88) Record dietary habits; milk main calcium source.	Habitual diet. Mean dietary calcium intake was 833 mg/day from all clinical trial participants Calcium group mean calcium intake was 1586 mg/day		Final number of participants used for analysis was 79, 100, and 85 for the calcium supplemented, placebo, and observational groups, respectively. Reported average pill compliance was 70.5% Pill compliance variability resulted in a wide-range of total calcium intake in the supplemented groups. Post-hoc stratification into subgroups according to cumulative total calcium intake about the median intake. The composition of the high and low subgroups was also varied.	BMD of the lumbar spine (L2 – L4) increased in all three groups from the average age of 15 to 18 years. No difference in BMD between the calcium and the placebo group (p=0.313). Supplemented group had 3% higher BMD at the femur trochanter (p=0.0024) and higher volumetric density at the proximal radius (1002 ± 7 mg/cm ³ than the placebo (990 ± 6 mg/day ³) and observational groups (996 ± 7 mg/day ³), but were not significantly different (p=0.41). Cross-sectional area of the proximal radius was much higher in the observational group than the clinical trial groups (p=0.008). However, volumetric BMD was higher in the calcium supplemented group (p=0.018).	The authors conclude that the relatively weak effects observed in this study were presumptively due to BMD established earlier during growth and maintained in the late adolescence and young adult periods. Calcium supplementation on top of habitual dietary calcium intake of approximately 830 mg/day did not influence BMD of the AP lumbar spine. The researcher then concluded that this study did indicate that calcium and dairy products influence bone mass acquisition.

Literature Citation	Study Design	Number and Description of Subjects	Duration of Study	Specifics of Intervention Including Source and Identity of Test Material	Base Diet	Additional Treatments	Other Factors Affecting Interpretation of Data	Results	Comments
Winters-Stone, K.M., <i>et al.</i> One year of oral calcium supplementation maintains cortical bone density in young adult female distance runners. <i>Int J Sport Nutr and Exercise Metab.</i> 2004; 14: 7	<p>Randomized, double-blind placebo controlled trial.</p> <p>Measured: BMD of the greater trochanter, femoral neck, lumbar spine (L2 - L4), and femoral mid-shaft by DXA; lean and fat mass from whole body scans; Anthropometric measurements of height and weight; 4-day food records analyzed by Food Processor II, v2.2 for total energy, carbohydrate, protein, fat, calcium, and phosphorous.</p>	<p>51 Healthy women with a mean age of 23.7 ± 4.7 years (range 18 - 35 years), mean height of 165 ± 6.3 cm and weight 55.7 ± 6.1 kg.</p> <p>Exclusion criteria: age younger than 18 or older than 35 years; ran at least 10 miles per week; non-participation in athletic competition; diseases known to affect bone metabolism; current medication regimens known to alter bone or bone metabolism</p>	12 months	<p><u>Experimental group</u> (N=13) 1000 mg daily calcium supplement in the form of a 500 mg chewable calcium carbonate tablet twice daily (one in the morning; one in the evening).</p> <p><u>Control group</u> (N=10) Sugar based placebo tablets taken twice daily like the experimental group.</p> <p>Both chewable calcium supplement tablets and placebo tablets were provided by SmithKline Beecham, Inc.</p>	<p>Habitual diet.</p> <p>Experimental group mean calcium intake was 1006 ± 454 mg/day.</p> <p>Control group mean calcium intake was 1294 ± 1263 mg/day.</p>		<p>Mean tablet compliance was 75% (79% for the experimental group and 71% for the placebo group, respectively).</p> <p>50% attrition rate due to a 7 month delayed delivery of supplements by the supplier, 14 women dropped out due to lack of interest. Another 14 dropped out over the trial period for the following reasons: stopped running due to injury (N=3), relocation outside study area (N=4), reduced interest (N=4), inability/unwillingness to travel to the study site (N=4). Final total was 23 women.</p>	<p>At baseline, mean BMD values across groups observed at the spine and hip were 4% below and 1% above age matched women from a DXA database.</p> <p>Calcium supplementation did not affect either hip or spine BMD. However, femoral mid-shaft BMD was maintained in the experimental group as compared to the control group ($p=0.02$). Adjustment of BMD response for significant changes in percent body fat by ANCOVA did not alter statistical outcomes.</p> <p>There were no significant group differences observed for any dietary variable. With supplementation, the participants of the experimental group received approximately 800 mg above their habitual calcium intake and approximately 500 mg more than their control group counterparts.</p>	<p>The researcher conclude that contrary to some expectations, female endurance runners do not have a superior skeletal status as compared to their sedentary counterparts, and it is likely that suboptimal nutrition may contribute to this finding. They further state that the repetitive nature of endurance running may increase bone turnover at stressed sites. The possibility exists that intervention raised calcium intake into the optimal range for cortical bone loss prevention for these women athletes.</p>