| **Author, Year,**  **Quality, Sample Size Analyzed Overall and by Study Group** | | **Duration**  **(Years)** | **Total Fractures**  **Risk or No. (%)** | | **Hip Fractures**  **Risk or No. (%)** | | **Nonvertebral Fractures**  **Risk or No. (%)** | | **Vertebral Fractures**  **Risk or No. (%)** | **Other Fractures**  **Risk or No. (%)** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Main Analysis** | |  |  | |  | |  | |  | |  |
| Dawson-Hughes et al, 1997[74](#_ENREF_74)  Fair  Total N=445 randomized (N analyzed=389) | | 3 years | NR | | ARD\*, -0.50% (-1.88% to 0.89%)  RR\*, 0.36 (0.01 to 8.78) | | 37(9.5\*)  ARD\*,-6.99% (95% CI,  -12.71% to -1.27%)  RR, 0.46 (95% CI, 0.23 to 0.90, p=0.02)  Fractures resulting from minimal or no trauma: 28 (7.2\*); RR, 0.40 (95% CI, 0.2 to 0.8)  Subgroups:  Women 32 (15.0)  Men 5 (2.8) | | NR | NR | |
| Placebo  n=202 | | -- | NR | | 1 (0.5\*) | | 26 (12.9)  Subgroups:  Women 22\* (19.6)  Men NR (NR) | | NR | NR | |
| Vitamin D3 700 IU orally plus elemental calcium 500 mg (as malate salt) daily  n=187 | | -- | NR | | 0 (0\*) | | 11 (5.9)  Subgroups:  Women 10\* (9.9)  Men NR (NR) | | NR | NR | |
| Khaw, Scragg et al, 2017[77](#_ENREF_77), [78](#_ENREF_78)  VIDA  Good  Total N=5,110 | | 3.3 years | NR | | NR | | ARD\*, 0.77% (-0.51% to 2.04%)  Adjusted HR, 1.19 (0.94 to 1.50) | | NR | NR | |
| Placebo  N analyzed=2,550 | | -- | NR | | NR | | 136 (5.3) | | NR | NR | |
| Vitamin D3 orally 200,000 IU initial dose followed by 100,000 IU every month  n=2,558 analyzed | | -- | NR | | NR | | 156 (6.1) | | NR | NR | |
| Komulainen et al, 1998[71](#_ENREF_71)  Komulainen et al, 1999[118](#_ENREF_118)  OSTPRE†  Fair  Total N=232 | | 5 years | NR | | ARD\*, -0.86% (95% CI,  -3.77% to 2.04%)  RR\* 0.50 (95% CI, 0.05 to 5.44) | | ARD\*, -3.45% (95% CI,  -11.55% to 4.66%)  Unadjusted RR, 0.72ǂ (95% CI, 0.22 to 1.56)  Adjusted§ RR, 0.64 (95% CI, 0.29 to 1.42) | | NR | -- | |
| Elemental calcium 93 mg (as lactate salt) daily  (no vitamin D placebo)  n=116 | | -- | NR | | 2 (1.7\*) | | 15 (12.9\*) | | NR | NR | |
| Vitamin D3 300 IU plus elemental calcium 93 mg (as lactate salt) dailyǁ  n=116 | | -- | NR | | 1 (0.9\*) | | 11 (9.5\*) | | NR | NR | |
| Lips et al, 1996[75](#_ENREF_75)  Fair  Total N=2,578 | | Median 3.5 years | NR | | ARD\*, 0.76% (95% CI,  -0.77% to 2.30%)  Unadjusted HR, 1.18 (95% CI, 0.81 to 1.71)¶  RR\*, 1.20 (95% CI, 0.83 to 1.75) | | NR | | NR | Total peripheral fractures:#  ARD\*, 0.21% (95% CI, 1.60% to 2.03%)  Unadjusted HR, 1.03 (95% CI, 0.75 to 1.40)  RR\*, 1.04 (95% CI, 0.76 to 1.41) | |
| Placebo  n=1,287 | | -- | NR | | 48 (3.7) | | NR | | NR | Total peripheral fractures#:74 (5.8)  Subtypes:  Colles fracture: 22 (1.7)  Humerus fracture: 12 (0.9)  Ankle/Foot/Leg fracture: 17 (1.3)  Other fracture: 23 (1.8) | |
| Vitamin D3 400 IU orally daily  n=1,291 | | -- | NR | | 58 (4.5) | | NR | | NR | Total peripheral fractures#: 77 (6.0)  Subtypes:  Colles fracture: 20 (1.5)  Humerus fracture: 10 (0.8)  Ankle/Foot/Leg fracture: 20 (1.5)  Other fracture: 27 (0.2) | |
| Recker et al, 1996[72](#_ENREF_72)  Fair  Total N=103 | | 4.3 years (1.1) | NR | | NR | | NR | | Morphometric:  ARD\*, 7.26% (95% CI, -9.84% to 24.36%)  RR\*, 1.34 (95% CI, 0.68 to 2.64) | NR | |
| Placebo  n=61 | | -- | NR | | NR | | NR | | Morphometric: 13 (21.3\*) | NR | |
| Calcium 1,200 mg (as carbonate salt) daily in 2 divided doses  n=42 | | -- | NR | | NR | | NR | | Morphometric: 12 (28.6\*) | NR | |
| Riggs et al, 1998[73](#_ENREF_73)  Fair  Total N=236 | | 4 years | NR | | NR | | ARD\*, -1.01% (95% CI,  -8.58% to 6.56%)  RR\*, 0.90 (95% CI, 0.41 to 1.96) | | Morphometric:  ARD\*, -0.97% (95% CI, -7.57% to 5.63%)  RR\*, 0.87 (95% CI, 0.35 to 2.19) | NR | |
| Placebo  n=117 | | -- | NR | | NR | | 12 (10.3) | | Morphometric fractures: 9 (7.7) | NR | |
| Calcium 1,600 mg (as citrate salt) daily in 4 divided doses  n=119 | | -- | NR | | NR | | 11 (9.2) | | Morphometric fractures: 8 (6.7) | NR | |
| Trivedi et al, 2003[76](#_ENREF_76)  Fair  Total N=2,686  (649 women; 2,037 men) | | 5 | ARD\*, -2.26% (95% CI, 4.53% to 0.00%)  Age-adjusted RR, 0.78 (95% CI, 0.61 to 0.99)  RR\*, 0.80 (95% CI, 0.63 to 1.00)  Subgroups:  Women: age-adjusted RR, 0.68 (95% CI, 0.46 to 1.01)  Men: age-adjusted RR, 0.83 (95% CI, 0.61 to 1.13) | | ARD\*, -0.23% (95% CI,  -1.20% to 0.74%)  Age-adjusted RR, 0.85 (95% CI, 0.47 to 1.53)  RR\*, 0.87 (95% CI, 0.49 to 1.56)  Subgroups:  Women: age-adjusted RR, 0.98 (95% CI, 0.41 to 2.36)  Men: age-adjusted RR, 0.76 (95% CI, 0.35 to 1.67) | | NR | | Clinical fractures:  ARD\*, -0.75% (95% CI, -1.73% to 0.23%)  Age-adjusted RR, 0.63 (95% CI, 0.35 to 1.14)  RR\*, 0.64 (95% CI, 0.36 to 1.15)  Subgroups:  Women: age-adjusted RR, 0.65 (95% CI, 0.18 to 2.30)  Men: age-adjusted RR, 0.62 (95% CI, 0.32 to 1.22) | Hip, wrist or forearm, or vertebrae fractures:  Age-adjusted RR, 0.67 (95% CI, 0.48 to 0.93)  Subgroups:  Women: Age-adjusted RR, 0.61 (95% CI, 0.37 to 1.02)  Men: Age-adjusted RR, 0.83 (95% CI, 0.61 to 1.13) | |
| Placebo  n=1,341  (323 women; 1,018 men) | | -- | 149 (11.1\*)  Subgroups:  Women: 58 (18.0\*)  Men: 91 (8.9\*) | | 24 (1.8\*)  Subgroups:  Women: 10 (3.1\*)  Men: 14 (1.4\*) | | NR | | Clinical fractures: 28 (2.1\*)  Subgroups:  Women: 6 (1.9\*)  Men: 22 (2.2\*) | Hip, wrist or forearm, or vertebrae fractures: 87 (6.5\*)  Subgroups:  Women: 37 (11.5\*)  Men: 50 (4.9\*) | |
| Vitamin D3 100,000 IU orally every 4 months  n=1,345  (326 women; 1,019 men) | | -- | 119 (8.8\*)  Subgroups:  Women: 42 (12.9\*)  Men: 77 (7.6\*) | | 21 (1.6\*)  Subgroups:  Women:10 (3.1\*)  Men:11 (1.1\*) | | NR | | Clinical fractures:  18 (1.3\*)  Subgroups:  Women: 4 (1.2\*)  Men: 14 (1.4\*) | Hip, wrist or forearm, or vertebrae fractures: 60 (4.5\*)  Subgroups:  Women: 24 (7.4\*)  Men: 36 (3.5\*) | |
| WHI Calcium and Vitamin D Trial\*\*  Fair  Total N=36,282 | | 7 years  (SD, 1.4) | ARD\*, -0.35% (95% CI, -1.02% to 0.31%)  HR, 0.96 (95% CI, 0.91 to 1.02) ††  RR\*, 0.97 (95% CI, 0.92 to 1.03)  Subgroups:  *Personal use of calcium or vitamin D supplements at baseline*[*97*](#_ENREF_97)  Nonusers: HR, 0.97 (95% CI, 0.88 to 1.07)  Users: HR, NR | | ARD\*, -0.14% (95% CI,  -0.34% to 0.07%)  HR, 0.88 (95% CI, 0.72 to 1.08)ǂǂ  RR\*, 0.88 (95% CI, 0.72 to 1.07)  Subgroups:  *Age 50 to 59*  HR, 2.17 (95% CI, 1.13 to 4.18)  *Age 60 to 60*  HR, 0.74 (95% CI, 0.52 to 1.06)  *Age 70 to 79*  HR, 0.82 (95% CI 0.62 to 1.08)  p for interaction=0.05  *Race/ethnic group*  p for interaction=0.87  *Prior fracture*  p for interaction 0.71  *Weight (<58 vs. ≥58 kg)*  p for interaction 0.44  *BMI (<25, 25-29, ≥30)*  p for interaction=0.36  *Sunlight exposure*  p for interaction 0.73  *No. of falls in prior 12 months*  0: HR, 0.74 (95% CI 0.56 to 0.98)  1: HR, 0.96 (95% CI 0.62 to 1.49)  2: HR, 1.16 (95% CI, 0.63 to 2.16)  ≥3: HR, 2.51 (95% CI, 0.97 to 6.48)  p for interaction=0.05  *Hormone therapy treatment assignment (WHI Trial)*  Placebo HR, 1.15 (95% CI, 0.81 to 1.63)  Active HR, 0.58 (95% CI 0.37 to 0.93)  p for interaction=0.07  *Personal use of calcium supplements at baseline*[*70*](#_ENREF_70)  None: HR, 0.70 (95% CI, 0.51 to 0.98)  <500 mg: HR, 0.87 (95% CI, 0.61 to 1.24)  *≥*500 mg: HR, 1.22 (95% CI, 0.83 to 1.79)  p for interaction=0.11  *Personal use of calcium or vitamin D supplements at baseline*[*97*](#_ENREF_97)  Nonusers: HR, 0.86 (95% CI, 0.62 to 1.20)  Users: HR, NR | | NR | | Clinical fractures:  ARD\*, -0.09% (95% CI, -0.30% to 0.12%)  HR, 0.90 (95% CI, 0.74 to 1.10)§§  RR\*, 0.92 (0.75 to 1.12) | Lower arm or wrist fracture:  ARD\*, 0.03% (95% CI,  -0.32% to 0.39%)  HR, 1.01 (95% CI,.90 to 1.14)  RR\*, 1.01 (95% CI, 0.90 to 1.13) | |
| Placebo  n=18,106 | | -- | 2,158 (11.9) | | 199 (1.1) | | NR | | Clinical fractures:  197 (1.1) | Lower arm or wrist fracture: 557 (3.1) | |
| Vitamin D 400 IU orally with 1,000 mg elemental calcium (as carbonate salt) in 2 divided doses daily  n=18,176 | | -- | 2,102 (11.6) | | 175 (1.0) | | NR | | Clinical fractures:  181 (1.0) | Lower arm or wrist fracture: 565 (3.1) | |
| Sensitivity Analysis |  | | |  | |  | |  |  | |  |
| Glendenning et al, 2012[86](#_ENREF_86)  Poor  Total N=686 | | 6 months/  9 months | ARD\*, -0.17% (95% CI, -2.69% to 2.35%)  RR\*, 0.94 (95% CI, 0.40 to 2.24)  p=1.00ǁǁ | | NR | | NR | | NR | NR | |
| Placebo¶¶  n=333 | | -- | 10\* (3.0)ǁǁ | | NR | | NR | | NR | NR | |
| Vitamin D3 150,000 IU orally at baseline, 3 months, and 6 months¶¶  n=353 | | -- | 10\* (2.8)ǁǁ | | NR | | NR | | NR | NR | |
| Peacock et al, 2000[85](#_ENREF_85)  Poor  Total N=438 randomized | | 4 years | NR | | NR | | Comparing vitamin D with placebo:  ARD\*, 3.20% (95% CI,  -3.66% to 10.06%)##  RR\*, 1.43 (95% CI, 0.66 to 3.11)##  Comparing calcium with placebo:  ARD\*, 1.32% (95% CI,  -5.30% to 7.94%)##  RR\*, 1.18 (95% CI, 0.52 to 2.68)## | | Both clinical and morphometric fractures:  Comparing vitamin D with placebo:  ARD\*, 4.76% (95% CI, -3.02% to 12.55%)##  RR\*, 1.49 (95% CI, 0.77 to 2.90)##  Comparing calcium with placebo:  ARD\*, -4.07% (95% CI, -10.46% to 2.31%)##  RR\*, 0.58 (95% CI, 0.24 to 1.40)## | NR | |
| Placebo  n=135  (98 women, 37 men) | | -- | NR | | NR | | 10 (7.4)  Subgroups:  Women: 9 (9.2\*)  Men: 1 (2.7\*) | | Both clinical and morphometric fractures: 13 (9.6)  Subgroups:  Women: 10 (10.2\*)  Men: 3 (8.1\*) | NR | |
| Vitamin D3  600 IU daily in 3 divided doses  n=132  (95 women, 37 men) | | -- | NR | | NR | | 14 (10.6)  Subgroups:  Women: 10 (10.5\*)  Men: 4 (10.8\*) | | Both clinical and morphometric fractures: 19 (14.4)  Subgroups:  Women: 15 (15.8\*)  Men: 4 (10.8\*) | NR | |
| Calcium 750 mg (as citrate malate salt) daily in 3 divided doses  n=126  (89 women, 37 men) | | -- | NR | | NR | | 11 (8.7)  Subgroups:  Women: 9 (10.1\*)  Men: 2 (5.4\*) | | Both clinical and morphometric fractures: 7(5.6)  Subgroups:  Women: 5 (5.6\*)  Men: 2 (5.4\*) | NR | |
| Prince et al, 2006,[89](#_ENREF_89) and Lewis et al, 2011[90](#_ENREF_90)  Calcium Intake Fracture Outcome Study  Fair  Total N=1,460 (N analyzed for morphometric fracture outcome=883) | | 5 years | Atraumatic fractures:  ARD\*, -2.19% (95% CI, -5.97% to 1.58%)  HR, 0.87 (95% CI, 0.67 to 1.12)  RR\*, 0.87 (95% CI, 0.69 to 1.10) | | Atraumatic fractures:  ARD\*, 0.68% (95% CI,  -0.42% to 1.78%);  HR, 1.84 (95% CI, 0.68 to 4.96);  RR\*, 1.83 (95% CI, 0.68 to 4.93) | | Atraumatic fractures:  ARD\*, -1.51% (95% CI,  -4.85% to 1.84%);  HR, 0.88 (95% CI, 0.65 to 1.18);  RR\*, 0.88 (95% CI, 0.67 to 1.16) | | Morphometric:  ARD\*, -0.86% (95% CI, -4.92% to 3.21%)  RR\*, 0.92 (95% CI, 0.63 to 1.35)  Atraumatic clinical:  ARD\*, -0.14% (95% CI, -2.43% to 2.16%)  HR, 0.98 (95% CI, 0.63 to 1.54);  RR\*,0.97 (95% CI, 0.63 to 1.51) | NR | |
| Placebo  n=730 | | -- | 126 (17.3) | | 6 (0.8) | | 94 (12.9) | | Morphometric:  50 (11.1)  Atraumatic clinical: 39 (5.3) | NR | |
| Elemental calcium 1,200 mg (as carbonate salt) daily in 2 divided doses  n=730 | | -- | 110 (15.1) | | 11 (1.5) | | 83 (11.4) | | Morphometric: 44 (10.2)  Atraumatic clinical: 38 (5.2) | NR | |
| Reid et al, 2006,[87](#_ENREF_87) Bolland et al, 2008[88](#_ENREF_88)  Fair  Total N=1,471 | | Reported by study groups only | ARD\*, -1.61% (95% CI, -5.45% to 2.24%)  HR, 0.91 (95% CI, 0.71 to 1.17)  RR\*, 0.91 (95% CI, 0.73 to 1.14) | | ARD\*, 1.65% (95% CI, 0.40% to 2.89%)  HR, 3.55 (95% CI, 1.31 to 9.63)  RR\*, 3.43 (95% CI, 1.27 to 9.26) | | NR | | Both clinical and morphometric fractures:  ARD\*, -1.45% (95% CI, -3.55% to 0.64%)  HR, 0.72 (95% CI, 0.44 to 1.18)  RR\*, 0.72 (95% CI, 0.44 to 1.16) | Major osteoporotic fractures:\*\*\*  ARD\*, -2.03% (95% CI,  -5.70% to 1.64%)  HR, 0.87 (95% CI, 0.67 to 1.14)  RR\*, 0.87 (95% CI, 0.69 to 1.11)  Distal forearm fracture:  HR, 0.64 (95% CI, 0.40 to 1.03) | |
| Placebo  n=739 | | 4.5 years | 132 (17.9\*) | | 5 (0.7\*) | | NR | | Both clinical and morphometric fractures: 38 (5.1\*) | Major osteoporotic fractures:\*\*\* 120 (16.2\*) | |
| Calcium 1,000 mg (as citrate sault) daily in 2 divided doses  n=732 | | 4.4 years | 119 (16.3\*) | | 17 (2.3\*) | | NR | | Both clinical and morphometric fractures: 27 (3.7\*) | Major osteoporotic fractures:\*\*\* 104 (14.2\*) | |
| Reid et al, 1995,[92](#_ENREF_92)  Reid et al, 1993[94](#_ENREF_94)  Poor  Total N=122 randomized in initial trial (78 used in analysis)††† | | 2 years | ARD\*, -4.92% (95% CI, -13.13% to 3.29%)  RR\*, 0.40 (95% CI, 0.08 to 1.98) | | NR | | NR | | NR | NR | |
| Placebo  n=61 | | -- | 5 (8.2\*) | | NR | | NR | | NR | NR | |
| Calcium 1,000 mg (as lactate-gluconate and carbonate salts) daily in 2 doses  n=61 | | -- | 2 (3.3\*) | | NR | | NR | | NR | NR | |
| Reid et al, 2008[91](#_ENREF_91)  Poor  Total N=323 | | 2 years | All fractures, regardless of mechanism of injuryǂǂǂ:  ARD\*, -2.85% (95% CI, -9.21% to 3.52%)  RR\*, 0.62 (95% CI, 0.21 to 1.83) for 600 mg compared with placebo  ARD\*, -3.77% (95% CI, -9.90% to 2.35%)  RR\*, 0.50 (95% CI, 0.15 to 1.60) for 1,200 mg compared with placebo | | NR | | NR | | NR | NR | |
| Placebo  n=107 | | -- | 8 (7.5\*) | | NR | | NR | | NR | NR | |
| Elemental calcium 600 mg (as citrate salt) daily  n=108 | | -- | 5 (4.6\*) | | NR | | NR | | NR | NR | |
| Elemental calcium 1,200 mg (as citrate salt) daily  n=108 | | -- | 4 (3.7\*) | | NR | | NR | | NR | NR | |
| Ruml et al, 1999[93](#_ENREF_93)  Poor  Total N=45 | | 2 | NR | | NR | | ARD and RR not calculable because of zero events in both groups | | NR | NR | |
| Placebo  n=28 | | -- | NR | | NR | | 0 (0) | | NR | NR | |
| Calcium 800 mg daily in 2 divided doses (as citrate salt)  n=17 | | -- | NR | | NR | | 0 (0) | | NR | NR | |
| Salovaara et al, 2010[106](#_ENREF_106)  Poor  Total N=3,195 | | Mean (SD) 3.0 (0.22) | ARD\*, -0.92% (95% CI, -2.49% to 0.64%)  Unadjusted HR, 0.85 (95% CI, 0.63 to 1.15)  Adjusted§§§ HR, 0.83 (95% CI, 0.61 to 1.12)  RR\*, 0.84 (95% CI, 0.63 to 1.13)  Subgroupsǁǁǁ | | ARD\*, 0.13% (95% CI,  -0.17% to 0.43%)  RR\*, 2.03 (95% CI, 0.37 to 11.06) | | ARD\*, -0.62% (95% CI,  -2.10% to 0.86%)  Unadjusted HR, 0.89 (95% CI, 0.65 to 1.22)  Adjusted§§§ HR, 0.87 (95% CI, 0.63 to 1.19)  RR\*, 0.88 (95% CI, 0.64 to 1.20)  Subgroupsǁǁǁ | | Clinical:  ARD\*, -0.24% (95% CI, -0.81% to 0.33%)  Unadjusted HR, 0.71 (95% CI, 0.3 to 1.66)  Adjusted§§§ HR, 0.67 (95% CI, 0.29 to 1.58)  RR\*, 0.70 (95% CI, 0.30 to 1.64)  Subgroupsǁǁǁ | Major osteoporotic fractures:  ARD\*, -0.58% (95% CI,  -1.75% to 0.59%)  Unadjusted HR, 0.83 (95% CI, 0.55 to 1.25)  Adjusted§§§ HR, 0.81 (95% CI, 0.54 to 1.22)  RR\*, 0.82 (95% CI, 0.55 to 1.22)  Subgroupsǁǁǁ | |
| Control (no placebo)  n=1,609 | | -- | 94 (5.8) | | 2 (0.1) | | 82 (5.1) | | Clinical fractures:  13 (0.8) | Major osteoporotic fractures: 52 (3.2) | |
| Vitamin D3 800 IU daily plus calcium 1,000 mg (as carbonate salt) daily in 2 divided doses  n=1,586 | | -- | 78 (4.9) | | 4 (0.2) | | 71 (4.5) | | Clinical fractures: 9 (0.6) | Major osteoporotic fractures: 42 (2.6) | |
| Sanders et al, 2010[83](#_ENREF_83)  Good  Total N=2,258 randomized (N=2,256 analyzed) | | Median 3 years | ARD\*, 2.59% (95% CI, -0.12% to 5.31%)  HR, 1.26 (95% CI, 0.99 to 1.59)  RR\*, 1.23 (95% CI, 0.99 to 1.54) | | ARD\*, 0.35% (-0.66% to 1.35%)  RR\*, 1.26 (95% CI, 0.64 to 2.47) | | ARD\*, 1.99% (95% CI,  -0.49% to 4.46%)  RR\*, 1.22 (95% CI, 0.95 to 1.57) | | Clinical:  ARD\*, 0.61% (95% CI, -0.75% to 1.96%)  RR\*, 1.24 (95% CI, 0.76 to 2.03) | Other fracture types reported by study groups | |
| Placebo  n=1,125 | | -- | 125 (11.1) | | 15 (1.3) | | 101 (9.0) | | Clinical:  28 (2.5) | Colles: 23 (2.0)  Other forearm: 7 (0.6)  Humerus: 14 (1.2)  Ribs: 7 (0.6)  Clavicle/Scapula: 1 (0.1)  Pelvis: 4 (0.4)  Upper leg/Patella: 6 (0.5)  Lower leg: 5 (0.4)  Ankle: 12 (1.1)  Foot/Toes: 12 (1.1)  Hand/Fingers: 3 (0.3)  Skull/Face: 4 (0.4) | |
| Vitamin D3 500,000 IU orally annually  n=1,131 | | -- | 155 (13.7) | | 19 (1.7) | | 124 (11.0) | | Clinical:  35 (3.1) | Colles: 26 (2.3)  Other forearm: 14 (1.2)  Humerus: 15 (1.3)  Ribs: 6 (0.5)  Clavicle/Scapula: 4 (0.4)  Pelvis: 8 (0.7)  Upper leg/Patella: 8 (0.7)  Lower leg: 6 (0.5)  Ankle: 8 (0.7)  Foot/Toes: 17 (1.5)  Hand/Fingers: 6 (0.5)  Skull/Face: 8 (0.7) | |
| Smith et al, 2007[84](#_ENREF_84)  Fair  Total N=9,440 | | 1 to 3 | NR | | Specified as “hip or femur”  ARD\*, 0.46% (-0.03% to 0.90%)  HR, 1.49 (95% CI, 1.02 to 2.18)  RR\*, 1.50 (95% CI, 1.02 to 2.19)  Subgroups:  Women: HR, 1.80 (95% CI, 1.12 to 2.90)  Men: HR, 1.02 (95% CI, 0.53 to 1.97) | | ARD\*, 0.55% (95% CI,  -0.42% to 1.53%)  HR, 1.09 (95% CI, 0.93 to 1.28)  RR\*, 1.09 (95% CI, 0.93 to 1.28)  Subgroups:  Women: HR, 1.21 (95% CI, 1.00 to 1.47)  Men: HR, 0.81 (95% CI, 0.59 to 1.11) | | NR | Wrist or radius, ulna, or Colles fracture:  ARD\*, 0.25% (95% CI,  -0.19% to 0.69%)  HR, 1.22 (95% CI, 0.85 to 1.76)  RR\*, 1.23 (95% CI, 0.85 to 1.77)  Subgroups:  Women: HR, 1.34 (95% CI, 0.91 to 1.98)  Men: HR, 0.50 (95% CI, 0.15 to 1.66) | |
| Placebo  n=4,713 | | -- | NR | | 44 (0.9)  Subgroups:  Women: 26 (1.0)  Men: 18 (0.8) | | 279 (5.9)  Subgroups:  Women: 194 (7.7)  Men: 85 (3.9) | | NR | Wrist or radius, ulna, or Colles fracture: 52 (1.1)  Subgroups:  Women: 44 (1.7)  Men: 8 (0.4) | |
| Vitamin D2 300,000 IU IM annually  n=4,727 | | -- | NR | | 66 (1.4)  Subgroups:  Women: 48 (1.9)  Men: 18 (0.8) | | 306 (6.5)  Subgroups:  Women: 238 (9.3)  Men: 68 (3.1) | | NR | Wrist or radius, ulna, or Colles fracture: 64 (1.4)  Subgroups:  Women: 60 (2.3)  Men: 4 (0.2) | |

\* Calculated based on data provided in the article.

† OSTPRE is a population-based study in Kuopio Province, Finland, that began in 1989 with mail recruitment of all women ages 47 to 56 years in the province, with 92.8% response to initial questionnaire. The study groups included in this evidence table are a subset of participants from OSTPRE who were recruited for the clinical trial in 1994. This trial also included two additional study groups that evaluated HT versus placebo (defined as the calcium-only group) and HT plus vitamin D3 versus placebo. These study groups were not eligible for this review.

ǂ Includes symptomatic fractures of distal radius/wrist, ankle, foot, toe, ribs, humerus, hip, skull, and patella.

§ Adjusted for baseline femoral neck BMD and previous fractures.

ǁ No intake during June-August. Dose of vitamin D reduced to 100 IU during the fifth treatment year because of observed adverse lipid change during vitamin D treatment.

¶ Adjustments for covariates, exclusion of participants who regularly used supplements, and restriction to subgroups including residents of apartment homes for the elderly, active treatment compliance, and age 80 years or older did not substantively change this estimate.

# Including Colles, humerus, ankle, foot, leg, and other (unspecified) fractures.

\*\* Results based on data provided across four publications, Jackson et al, 2006[70](#_ENREF_70); Prentice et al, 2013[97](#_ENREF_97); Bolland et al, 2011b[96](#_ENREF_96); and Robbins et al, 2014.[98](#_ENREF_98)

†† Subgroup analyses: HR 0.98 (95 % CI 0.89 to 1.07) among nonusers of personal supplements at baseline, HR 0.96 (95% CI 0.89 to 1.04) among users of supplements at baseline, p for interaction between treatment allocation and user of personal supplements at baseline=0.72.[96](#_ENREF_96) Sub group analyses among participants randomized to hormone therapy groups of the WHI Hormone Therapy RCT; HR not reported by these subgroups but p for interaction between hormone therapy use and nonuse and treatment allocation was=0.97.[98](#_ENREF_98)

ǂǂ Subgroup analyses: HR 0.85 (95% CI, 0.61 to 1.17) among nonusers of personal supplements at baseline, HR 0.93 (95% CI, 0.71 to 1.21) among users of personal supplements at baseline. P for interaction between treatment allocation (vitamin D and calcium versus placebo) and personal supplement use at baseline=0.65.[96](#_ENREF_96) Subgroup analyses among participants randomized to hormone therapy groups of the WHI Hormone Therapy RCT: HR 0.59 (95% CI 0.38 to 0.93) among participants randomized to active hormone therapy; HR 1.20 (95% CI, 0.85 to 1.69) among participants randomized to placebo hormone therapy. P for interaction between treatment allocation (vitamin D and calcium versus placebo) and hormone therapy use=0.01.[98](#_ENREF_98)

§§ Excludes cervical vertebral fractures. Subgroup analyses among participants randomized to hormone therapy groups of the WHI Hormone Therapy RCT; HR not reported by these subgroups but p=0.79[98](#_ENREF_98) for interaction between hormone therapy use and nonuse and treatment allocation (vitamin D and calcium versus placebo).

ǁǁ Fractures were reported in a diary and coded using the International Classification of Primary Care (ICPC2 Plus) system database of disease coding; no additional description or details were reported. Fractures were considered as adverse events, not efficacy endpoints.

¶¶ Cointerventions: Both groups received written lifestyle advice on maintaining physical activity (optimally 30 minutes per day outside) and consuming 1,300 mg calcium per day using diet and/or supplements.

## There were no significant sex main-effects or sex-by-treatment interactions in any of the variables; thus, men and women were combined in the analysis.

\*\*\* Major osteoporotic fractures are defined as all fractures except those of the head, hands, feet, and ankles, and that result from major trauma.

††† Based on 78 of the original 122 participants who completed the first 2 years of the trial.

ǂǂǂ Fractures were specified as adverse events in the protocol and were not specified as to site. All fractures except for toe fractures were noted to have occurred after substantial trauma.

§§§ Adjusted for age, BMI, smoking, use of alcohol, prior fracture, parental hip fracture, steroid use, diagnosed rheumatoid arthritis, and secondary osteoporosis.

ǁǁǁ No statistically significant difference between any of the subgroups analyzed. This includes age, calcium intake <700 mg/d, compliance levels, and exclusion of subjects with secondary osteoporosis.

**Abbreviations:** ARD=absolute risk difference; BMI=body mass index; CI=confidence interval; HR=hazard ratio; IU=international units; mg=milligram; N=Number; NR=not reported; RR=relative risk; WHI=Women’s Health Initiative.