| **Author, Year, Quality, and Sample Size Analyzed** | | **Duration**  **(years)** | **All-Cause Mortality**  **Risk or No. (%)** | | **Incident CVD or Stroke**  **Risk or No. (%)** | | **Incident Cancer**  **Risk or No. (%)** | | | **Incident Kidney Stones**  **Risk or No. (%)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Main Analysis |  | | |  | |  | |  |  | |
| Khaw, Scragg et al, 2017[77](#_ENREF_77), [78](#_ENREF_78)  VIDA  Good  Total N=5,110 | | 3.3 | ARD, -0.33% (-1.16% to 0.51%)\*;  RR, 0.87 (0.61 to 1.24) | | MI:  ARD, -0.12% (-0.71% to 0.47%)\*  HR, 0.90 (0.54 to 1.50)  Stroke:  ARD -0.04 % (-0.60% to 0.51%)\*  HR, 0.95 (0.55 to 1.62)  VTE:  ARD -0.16% (-0.55% to 0.23%)\*  HR, 0.74 (0.34 to 1.61)  Heart failure:  ARD, 0.46% (-0.39% to 1.31%)\*  HR, 1.19 (0.84 to 1.68) | | -- | | | -- |
| Placebo  n analyzed=2,550 | | -- | 65 (2.5%) | | MI: 31 (1.2%)  Stroke, hemorrhage, infarct:27(1.1%)  VTE: 15 (0.6%)  Heart failure: 57 (2.2%) | | -- | | | -- |
| Vitamin D3 orally200,000 IU initial dose followed by 100,000 IU every month n analyzed=2,558 | | -- | 58 (2.3%) | | MI: 28(1.1%)  Stroke, hemorrhage, infarct: 26 (1.0%)  VTE: 11 (0.4%)  Heart failure: 69 (2.7%) | | -- | | | -- |
| Komulainen et al, 1998,[71](#_ENREF_71) Komulainen et al, 1999[118](#_ENREF_118)  OSTPRE†  Fair  Total N=232 | | 5 | ARD\*, -0.87% (-3.26% to 1.52%)  RR\*, 0.34 (0.01 to 8.31) | | Myocardial infarction or coronary bypass operation:  ARD\*, 1.79% (-1.18% to 4.75%)  RR\*, 5.13 (0.25 to 105.73) | | Malignancies, including breast, ventricle, melanoma, endometrial, and cervical:  ARD\*, -0.82% (95% CI,  -4.63% to 2.99%);  RR\*, 0.68 (95% CI, 0.12 to 4.02) | | | NR |
| Elemental calcium 93 mg (as lactate salt) daily(no vitamin D placebo)  n analyzed=115 | | -- | 1 (0.9\*) | | 0 (0\*) | | 3 (2.6\*) | | | -- |
| Vitamin D3 300 IU plus elemental calcium 93 mg daily (salt not specified)ǂ  n analyzed=112 | | -- | 0 (0\*) | | 2 (1.8\*) | | 2 (1.8\*) | | | -- |
| Lappe et al, 2007[107](#_ENREF_107)  Good for cancer outcomes; Fair for kidney stone outcome  Total N=1,180 randomized, 1,179 analyzed | | 4 | NR | | NR | | Total cancers§ (excluding skin):  ARD\*, -3.12% (95% CI,  -6.56% to 0.31%)  RR\*, 0.55 (95% CI, 0.29 to 1.03)for calcium compared to placebo  ARD\*, -4.03% (95% CI,  -7.35% to -0.70%)  RR\*, 0.42 (95% CI, 0.21 to 0.83) for vitamin D with calcium compared with placebo  Breast cancer:  ARD\*, -1.43% (-3.61% to 0.75%)  RR\*, 0.49 (0.17 to 1.38)comparing calcium to placebo  ARD\*, -1.66% (-3.79% to 0.48%)  RR\*, 0.40 (0.13 to 1.22) comparing vitamin D with calcium to placebo  Colorectal cancer:  ARD\*, -0.69% (-1.81% to 0.42%)  RR\*, 0.13 (0.01 to 2.69) comparing calcium to placebo  ARD\*, -0.47% (-1.52% to 0.58%)  RR\*, 0.32 (0.03 to 3.54)comparing vitamin D with calcium to placebo | | | ARD\*, 0.33% (95% CI,  -0.69% to 1.35%)  RR\*, 1.94 (95% CI, 0.20 to 18.57) for calcium compared with placebo;  ARD\*, -0.12% (95% CI, -0.93% to 0.69%)  RR\*, 0.65 (95% CI, 0.04 to 10.28) for vitamin D with calcium compared with placebo |
| Placebo  n=288 | | -- | -- | | -- | | Total cancers (excluding skin): 20 (6.9)  Breast: 8 (2.8)  Colorectal: 2 (0.7) | | | 1 (0.4) |
| Calcium 1,400 mg daily (as citrate salt) or 1,500 mg daily (as carbonate salt) with vitamin D placebo  n=445 | | -- | -- | | -- | | Total cancers (excluding skin): 17 (3.8)  Breast: 6 (1.4)  Colorectal: 0(0) | | | 3 (0.7) |
| Calcium 1,400 mg daily (as citrate salt) or 1,500 mg daily (as carbonate salt) with vitamin D3 1,000 IU orally daily  n=446 | | -- | -- | | -- | | Total cancers (excluding skin): 13 (2.9)  Breast: 5 (1.1)  Colorectal: 1 (0.2) | | | 1 (0.2) |
| Lappe et al, 2017[108](#_ENREF_108)  Fair  Total N=2,303 randomized, 2,197 analyzed | | 4 | ARD\*, -0.19% (-0.90% to 0.52%);  RR\*, 0.77 (0.29 to 2.07) | | NR | | Total excluding nonmelanoma skin cancer:  ARD\*, -1.76% (-3.58% to 0.05%)  RR\*, 0.70 (95% CI, 0.48 to 1.01)  Breast cancer:  ARD\*, -0.65% (-1.75% to 0.46%)  RR\*, 0.69 (95% CI, 0.37 to 1.30)  Colorectal cancer:  ARD\*, 0.00% (-0.51% to 0.50%)  RR\*, 0.99 (95% CI, 0.25 to 3.96) | | | ARD\*, 0.54% (-0.36% to 1.44%)  RR\*, 1.59 (0.72 to 3.49) |
| Placebo (n analyzed=1,095) | | -- | 9 (0.8%) | | -- | | Total: 64 (5.8%)  Breast: 23 (2.1%)  Colorectal: 4 (0.4%) | | | 10 (0.9%) |
| Vitamin D3 2,000 IU orally daily with 1,500 mgcalcium daily (as carbonate salt)  (n analyzed=1,102) | | -- | 7 (0.6%) | | -- | | Total: 45 (4.1%)  Breast: 16 (1.5%)  Colorectal 4 (0.4%) | | | 16 (1.5%) |
| Lips et al, 1996[75](#_ENREF_75)  Fair  N=2,578 | | Median 3.5 | ARD\*, -1.93% (95% CI, -5.17% to 1.31%)  RR\*, 0.92 (95% CI, 0.80 to 1.06) | | NR | | NR | | | NR |
| Placebo  n=1,287 | | -- | 306 (23.8) | | -- | | -- | | | -- |
| Vitamin D3 400 IU orally daily  n=1,291 | | -- | 282 (21.8) | | -- | | -- | | | -- |
| Reid et al, 2008[91](#_ENREF_91)  Fair  Total N randomized=323, n analyzed=290ǁ | | 2 | ARD\*, -0.02% (-2.65% to 2.61%)  RR\*, 0.98 (95% CI, 0.06 to 15.48) for 600 mg compared with placebo  ARD\*, 0.05% (-2.67% to 2.77%)  RR\*, 1.05 (95% CI, 0.07 to 16.57) for 1,200 mgcompared with placebo | | Myocardial Infarction as a protocol-specified adverse event:  ARD\*, 1.02% (-1.75% to 3.80%)  RR\*, 3.03 (95% CI, 0.12 to 73.49) for 600 mg compared with placebo  ARD\*, 2.15% (-1.38% to 5.68%)  RR\*, 5.32 (95% CI, 0.26 to 109.35) for 1,200 mg compared with placebo | | NR | | | Renal calculus as a protocol-specified adverse event  ARD\*, -1.01% (-3.77% to 1.75%)  RR\*, 0.34 (95% CI, 0.01 to 8.17) for 600 mg compared with placebo  ARD\*, -1.01% (-3.81% to 1.79%)  RR\*, 0.35 (95% CI, 0.01 to 8.60) for 1,200 mg compared with placebo |
| Placebo  n=99 (104 for mortality) | | -- | 1 (0.96) | | 0 (0) | | -- | | | 1 (1.0) |
| Elemental calcium 600 mg (as citrate salt) daily  n=98 (106 for mortality) | | -- | 1 (0.94) | | 1 (1.0) | | -- | | | 0 (0) |
| Elemental calcium 1,200 mg (as citrate salt) daily  n=93 (99 for mortality) | | -- | 1 (1.0) | | 2 (2.2) | | -- | | | 0 (0) |
| Riggs et al, 1998[73](#_ENREF_73)  Fair  Total N=236 | | 4 | NR | | NR | | NR | | | ARD\*, -0.85% (95% CI,  -3.18% to 1.47%)  RR\*, 0.33 (95% CI, 0.01 to 7.97) |
| Placebo  n=117 | | -- | -- | | -- | | -- | | | 1 (0.9) |
| Calcium 1,600 mg daily in 4 divided doses (as citrate salt)  n=119 | | -- | -- | | -- | | -- | | | 0 (0) |
| Trivedi et al, 2003[76](#_ENREF_76)  Fair  Total N=2,686 | | 5 | ARD\*, -1.76% (95% CI, -4.64% to 1.11%)  Age-adjusted RR, 0.88 (95% CI, 0.74 to 1.06);  RR\*, 0.90 (95% CI, 0.77 to 1.07)  Subgroups:  Women:  ARD\*, -0.69% (95% CI, -4.87% to 3.49%)  RR\*, 0.92 (95% CI, 0.54 to 1.55)  Men:  ARD\*, -2.08% (95% CI, -5.59% to 1.43%);  RR\*, 0.90 (95% CI, 0.76 to 1.07) | | Total CVD:  ARD\*, -2.04% (95% CI, -5.68% to 1.60%)  Age-adjusted RR, 0.90 (95% CI, 0.77 to 1.06)  RR\*, 0.95 (95% CI, 0.86 to 1.04)  Ischemic heart disease:  ARD\*, -0.72% (95% CI, -3.56% to 2.12%)  Age-adjusted RR, 0.94 (95% CI, 0.77 to 1.15)  RR\*, 0.96 (95% CI, 0.81 to 1.13)  Cerebrovascular disease:  ARD\*, 0.27% (95% CI, -1.74% to 2.29%)  Age-adjusted RR, 1.02 (95% CI, 0.77 to 1.36)  RR\*, 1.04 (95% CI, 0.80 to 1.35)  Subgroups:  Women:  Ischemic heart disease:  ARD\*, -2.26% (95% CI, -7.12% to 2.60%); RR\*, 0.82 (95% CI, 0.53 to 1.26)  Cerebrovascular disease:  ARD\*, 0.87% (95% CI, -2.60% to 4.35%); RR\*, 1.18 (95% CI, 0.62 to 2.25)  Men:  Ischemic heart disease:  ARD\*, -0.21% (95% CI, -3.61% to 3.18%); RR\*, 0.99 (95% CI, 0.83 to 1.18)  Cerebrovascular disease:  ARD\*, 0.09% (95 % CI, -2.32% to 2.50%); RR\*, 1.01 (95% CI, 0.76 to 1.35) | | Any cancer:  ARD\*, 1.08% (-1.50% to 3.66%)  Age-adjusted RR, 1.09 (95% CI, 0.86 to 1.36)¶  RR\*, 1.08 (95% CI, 0.89 to 1.31)  Any cancer (excluding skin):  ARD\*, 1.01% (95% CI, -1.28% to 3.30%)  Age-adjusted RR, 1.11 (95% CI, 0.86 to 1.42)#  RR\*,1.10 (0.88 to 1.38)  Colon cancer:  ARD\*, 0.07% (-1.00% to 1.14%)  Age-adjusted RR, 1.02 (95% CI, 0.60 to 1.74)\*\*  RR\*, 1.03 (95% CI, 0.61 to 1.74)  Respiratory:  ARD\*, 0.15% (95% CI, -0.68% to 0.97%)  Age-adjusted RR, 1.12 (95% CI, 0.56 to 2.25)††  RR\*, 1.13 (95% CI, 0.57 to 2.25)  Subgroups:  Any cancer  Women: ARD\*, -0.38% (95% CI, -4.52% to 3.76%)  RR\*, 0.95 (95% CI, 0.56 to 1.61)  Men: ARD\*, 1.56% (95% CI,  -1.56% to 4.67%)  RR,\* 1.11 (95% CI, 0.90 to 1.36) | | | NR |
| Placebo  n=1,341 | | -- | 247 (18.4)  Women 27 (8.4)  Men 220 (21.6) | | Total CVD:503 (37.5)  Ischemic heart disease:233 (17.4)  Women: 40 (12.4)  Men: 193 (19.0)  Cerebrovascular disease:101 (7.5)  Women: 16 (5.0)  Men: 85 (8.4) | | Any cancer:173 (12.9)  Women: 26 (8.1)  Men: 147 (14.4)  Any cancer (excluding skin):  130 (9.7)  Colon cancer:27 (2.0)  Respiratory cancer:15 (1.1) | | | -- |
| Vitamin D3 100,000 IU orally every 4 months  n=1,345 | | -- | 224 (16.7)  Women 25 (7.7)  Men 199 (19.5) | | CVD:477 (35.5)  Ischemic heart disease:224 (16.7)  Women: 33 (10.1)  Men: 191 (18.7)  Cerebrovascular disease:105 (7.8)  Women: 19 (5.8)  Men: 86 (8.4) | | Any cancer:188 (14.0)  Women: 25 (7.7)  Men: 163 (16.0)  Any cancer (excluding skin):  144 (10.7)  Colon cancer:28 (2.1)  Respiratory cancer:17 (1.3) | | | -- |
| WHI Calcium and Vitamin D Trialǂǂ  Fair  Total N=36,282 | | 7 | ARD\*, -0.36% (-0.78% to 0.05%)  HR, 0.91 (95% CI, 0.83 to 1.01)  RR\*, 0.92 (95% CI, 0.83 to 1.01)  No significant differences based on age (<70 years vs. ≥70 years, use of personal supplements at baseline, or race/ethnicity)§§ | | Total CVD:  ARD\*, 0.08% (95% CI, -0.54% to 0.70%)  HR, 1.00 (95% CI, 0.94 to 1.07)  RR\*, 1.01 (95% CI, 0.95 to 1.07)  No differences based on use of personal supplements at baseline.ǁǁ  Myocardial infarction:  ARD\*, 0.11% (95 % CI, -0.20% to 0.41%)  HR, 1.03 (95% CI, 0.90 to 1.19)  RR\*, 1.05 (95% CI, 0.92 to 1.20)  Some differences based on personal supplement use at baseline¶¶  Coronary heart disease (defined as MI or CHD death):  ARD\*, 0.12% (95% CI, -0.21% to 0.45%)  HR, 1.03 (95% CI, 0.90 to 1.17)  RR\*,1.05 (95% CI, 0.92 to 1.18)  No differences based on personal supplement use at baseline and no differences by age##  Stroke:  ARD\*, -0.09% (95% CI, -0.38% to 0.20%)  HR, 0.95 (95% CI, 0.82 to 1.10)  RR\*, 0.96 (95% CI, 0.83 to 1.10)  Some differences based on personal supplement use at baseline\*\*\*  Heart failure hospitalization:  ARD\*, -0.11% (95% CI, -0.40% to 0.18%)  HR, 0.95 (95% CI, 0.82 to 1.09)†††  RR\*, 0.95 (95% CI, 0.82 to 1.09)  VTE (includes deep vein thrombosis and pulmonary embolus that were considered idiopathic or secondary events):  ARD\*, -0.16% (95% CI, -0.44% to 0.12%)  HR, 0.92 (95% CI, 0.79 to 1.07)  RR\*,0.92 (95% CI, 0.79 to 1.06)  Deep vein thrombosis:  ARD\*, -0.06% (95% CI, -0.30% to 0.18%)  HR, 0.97 (95% CI, 0.82 to 1.16)  RR\*, 0.96 (95% CI, 0.80 to 1.14)  Pulmonary embolism:  ARD\*, -0.08% (95% CI, -0.26% to 0.10%)  HR, 0.92 (95% CI, 0.73 to 1.16)  RR\*, 0.90 (95% CI, 0.72 to 1.14)  Idiopathic VTE:  HR, 0.62 (95% CI, 0.42 to 0.92)ǂǂǂ  Secondary VTE:  HR, 0.98 (95% CI, 0.83 to 1.16) | | Total invasive cancer:  ARD\*, -0.28% (95% CI,  -0.82% to 0.27%)  HR§§§ 0.96 (95% CI, 0.89 to 1.04)  RR\*, 0.96 (95% CI, 0.90 to 1.04)  No differences among age groups, race/ethnicity, or when limited toparticipants with no prior history of invasive cancer. Some differences based on personal supplement use at baselineǁǁǁ  Breast cancer:  ARD\*, -0.11% (95% CI,  -0.46% to 0.24%)  HR, 0.96 (95% CI, 0.85 to 1.08)  RR\*, 0.96 (95% CI, 0.86 to 1.08)  Some differences based on personal supplement use at baseline¶¶¶  Colorectal cancer:  ARD\*, 0.07% (95% CI,  -0.12% to 0.27%)  HR, 1.06 (95% CI, 0.85 to 1.32) ###  RR\*, 1.09 (95% CI, 0.87 to 1.35)  Some differences based on personal supplement use at baseline\*\*\*\*  Nonmelanoma skin cancer:  ARD\*, 0.12% (95% CI,  -0.48% to 0.71%)  HR, 1.02 (95% CI, 0.95 to 1.07)  RR\*, 1.01 (95% CI, 0.95 to 1.08)  Melanoma skin cancer:  ARD\*, -0.07% (95% CI,  -0.21% to 0.07%)  HR, 0.86 (95% CI, 0.64 to 1.16)  RR\*, 0.87 (95% CI, 0.65 to 1.17)  Some differences based on history of nonmelanoma skin cancer.†††† | | | ARD\*, 0.37% (95% CI, 0.06% to 0.67%)  RR, 1.17 (95% CI, 1.03 to 1.34)  No differences by age or race/ ethnicity.‡‡‡‡ |
| Placebo  n=18,106 | | -- | 807 (4.5) | | Total CVD: 1,810 (10.0)  Myocardial infarction: 390 (2.2)  Coronary heart disease (defined as MI or CHD death): 475 (2.6)  Stroke: 377 (2.1)  Heart failureamong participants without a history of heart failure at baseline: 381 (2.1)  VTE: 348 (1.9)  Deep vein thrombosis: 256 (1.4)  Pulmonary embolism: 149 (0.8) | | Total invasive cancer: 1,411 (7.8)  Breast cancer: 546 (3.0)  Colorectal cancer:154 (0.9)  Melanoma skin cancer: 94 (0.5)  Nonmelanoma skin cancer: 1,655 (9.1) | | | 381 (2.1) |
| Calcium 1,000 mg daily in 2 divided doses as carbonate salt plus vitamin D3 400 IU orally daily in 2 divided doses  n=18,176 | | -- | 744 (4.1) | | Total CVD: 1,832 (10.1)  Myocardial infarction: 411 (2.3)  Coronary heart disease (defined as MI or CHD death): 499 (2.8)  Stroke: 362 (2.0)  Heart failureamong participants without a history of heart failure at baseline: 363 (2.0)  VTE: 320 (1.8)  Deep vein thrombosis: 246 (1.4)  Pulmonary embolism: 135 (0.7) | | Total invasive cancer: 1,366 (7.5)  Breast cancer: 528 (2.9)  Colorectal cancer: 168 (0.9)  Melanoma skin cancer: 82 (0.5)  Nonmelanoma skin cancer:  1,683 (9.3) | | | 449 (2.5) |
| Sensitivity Analysis | |  | |  | |  | |  |  | |
| Aloia et al, 2005[114](#_ENREF_114)  Poor  Total N=208 | | 3 | NR | | NR | | NR | | | ARD and RR not calculable because of zero events in both groups |
| Placebo, plus some participants in this group received an unknown dose of calcium  n=104 | | -- | -- | | -- | | -- | | | 0 (0) |
| Vitamin D3 1,200 IU orally daily during the first 24 months, increasing to 2,000 IU daily thereafter, plus some participants in this group received an unspecified dose of calcium  n=104 | | -- | -- | | -- | | -- | | | 0 (0) |
| Cherniack et al, 2011[119](#_ENREF_119)  Poor  Total N=34 | | 6 months | NR | | Myocardial infarction:  ARD\*, 0.00% (95% CI, -15.82% to 15.82%)  RR\*, 1.00 (95% CI, 0.07 to 14.72) | | NR | | | NR |
| Placebo, plus most also received an unspecified dose of a calcium supplement  n=17 | | -- | -- | | 1 (5.8) | | -- | | | -- |
| Vitamin D3 2,000 IU orally daily, plus most also received an unspecified dose of a calcium supplement  n=17 | | -- | -- | | 1 (5.8) | | -- | | | -- |
| Glendenning et al, 2012[86](#_ENREF_86)  Poor  Total N=686 | | 9 months | NR | | Stroke:  ARD\*, 0.25% (95% CI, -1.02% to 1.52%)  RR\*, 1.42 (95% CI, 0.24 to 8.42)  Ischemic heart disease:  ARD\*, -0.63% (95% CI, -2.04% to 0.77%)  RR\*,0.47 (95% CI, 0.09 to 2.56) | | RR\*, 1.19 (95% CI, 0.62 to 2.31) | | | NR |
| Placebo§§§§  n=333 | | -- | -- | | Stroke: 2\* (0.6)  Ischemic heart disease: 4 (1.2) | | 15\* (4.5) | | | -- |
| Vitamin D3 150,000 IU orally at baseline, 3 months, and 6 months§§§§  n=353 | | -- | -- | | Stroke: 3\* (0.8)  Ischemic heart disease: 2\* (0.6) | | 19\* (5.4) | | | -- |
| Hin et al, 2017[110](#_ENREF_110) | | 1 | 4,000 IU or 2,000 IU vs. placebo  ARD\*, -2.97% (95% CI, -6.75% to 0.81%)  RR\*, 0.14 (95% CI, 0.01 to 2.70) | | Not eligible, poor quality | | Not eligible, poor quality | | | NR |
| Placebo | | -- | 3 (3.0) | | -- | | -- | | | -- |
| Vitamin D3 4,000 IU daily | | -- | 0 (0) | | -- | | -- | | | -- |
| Vitamin D3 2,000 IU daily | | -- | 0 (0) | | -- | | -- | | | -- |
| Peacock et al, 2000[85](#_ENREF_85)  Poor  Total N=377 | | 4 | NR | | NR | | NR | | | ARD\*, 0.81% (95% CI,  -1.38% to 2.990%)  RR\*, 3.12 (95% CI, 0.13 to 75.87) comparing calcium to placebo.  ARD and RR not calculable for the vitamin D vs placebo comparison due to zero events in both groups. |
| Placebo  n=129 | | 4 | -- | | -- | | -- | | | 0 (0) |
| Vitamin D3  600 IU daily in 3 divided doses  n=124 | | -- | -- | | -- | | -- | | | NA |
| Calcium 750 mg (as citrate malate salt) daily in 3 divided doses  n=124 | | -- | -- | | -- | | -- | | | 1 (0.8) |
| Prince et al, 2006,[89](#_ENREF_89) andLewis et al, 2011[90](#_ENREF_90)  Calcium Intake Fracture Outcome Study  Fair  Total N=1,460 | | 5 | ARD\*, -1.23% (95% CI, -3.38% to 0.91%)  RR\*, 0.76 (95% CI, 0.48 to 1.22) | | Incident ischemic heart disease diagnosis:  ARD\*, 0.68% (95% CI, -1.99% to 3.36%)  HR, 1.12 (95% CI, 0.77 to 1.64)  RR\*, 1.10 (95% CI, 0.76 to 1.58)  Atherosclerotic vascular disease hospitalization or death:  ARD\*, 0.20% (95% CI, -3.17% to 3.56%)  Adjusted HR, 0.94 (95% CI, 0.69 to 1.28)  RR\*, 1.01 (95% CI, 0.79 to 1.31)  Atherosclerotic vascular hospitalization:  ARD\*, 0.00% (95% CI, -3.39% to 3.39%)  RR\*, 1.00 (95% CI, 0.76 to 1.31)  Atherosclerotic vascular death:  ARD\*, -0.81% (95% CI, -2.60% to 0.98%)  RR\*, 0.76 (95% CI, 0.42 to 1.39) | | NR | | | ARD\*, 0.00% (95% CI, -0.54% to 0.54%)  RR\*, 1.00 (95% CI, 0.14 to 7.08) |
| Placebo  n=730 | | -- | 38 (5.2) | | Incident ischemic heart disease diagnosis: 51 (7.0)  Atherosclerotic vascular disease hospitalization or death: 103 (14.1)  Atherosclerotic vascular death: 24 (3.3)  Atherosclerotic vascular hospitalization: 91 (12.5) | | -- | | | 2 (0.3) |
| Elemental calcium 1,200 mg (as carbonate salt) daily in 2 divided doses  n=730 | | -- | 29 (4.0) | | Incident ischemic heart disease diagnosis: 56 (7.7)  Atherosclerotic vascular disease hospitalization or death: 104 (14.2)  Atherosclerotic vascular death: 18 (2.5)  Atherosclerotic vascular hospitalization: 91 (12.5) | | -- | | | 2 (0.3) |
| Recker et al, 1996[72](#_ENREF_72)  Poor  Total N=103 | | 4.3 | NR | | NR | | NR | | | NR |
| Placebo  n=61 | | -- | -- | | -- | | -- | | | 0 (0) |
| Calcium 1,200 mg (as carbonate salt) daily in 2 divided doses  n=42 | | -- | -- | | -- | | -- | | | 0 (0) |
| Reid et al, 2006[87](#_ENREF_87); Bolland et al, 2008[88](#_ENREF_88)  Fair  Total N=1471 | | 4.5 | ARD\*, 0.72% (95% CI, -1.35% to 2.79%)  RR\*, 1.18 (95% CI, 0.73 to 1.92) | | Myocardial infarction:  ARD\*, 1.39% (95% CI, -0.49% to 3.28%)  RR\*, 1.49 (95% CI, 0.86 to 2.57)  Stroke:  ARD\*, 1.26% (95% CI, -0.74% to 3.27%)  RR\*, 1.37 (95% CI, 0.83 to 2.28)  Myocardial infarction/Stroke composite outcome:  ARD\*, 1.43% (95% CI, -1.26% to 4.12%)  RR\*, 1.21 (95% CI, 0.84 to 1.74) | | NR | | | ARD\*, -0.27% (95% CI, -0.92% to 0.38%)  RR\*, 0.50 (95% CI, 0.09 to 2.75) |
| Placebo  n=739 | | -- | 29 (3.9) | | Myocardial infarction:21 (2.8)  NR for subgroup  Stroke:25 (3.4)  NR for subgroup  Myocardial infarction/Stroke composite outcome:50 (6.8) | | -- | | | 4 (0.5) |
| Calcium 1,000 mg (as citrate salt) daily in 2 divided doses  n=732 | | -- | 34 (4.6) | | Myocardial infarction:31 (4.2)  NR for subgroup  Stroke:34 (4.6)  NR for subgroup  Myocardial infarction/Stroke composite outcome:60 (8.2) | | -- | | | 2 (0.3) |
| Reid et al, 1995,[92](#_ENREF_92) Reid et al, 1993[94](#_ENREF_94)  Poor  Total N=122 | | 2 | NR | | NR | | NR | | | ARD\*, 1.64% (95% CI,  -2.79% to 6.06%)  RR\*, 3.00 (95% CI, 0.12 to 72.23) |
| Placebo  Initial trial: n=61 | | -- | -- | | -- | | -- | | | 0ǁǁǁǁ |
| Calcium 1,000 mg (as lactate-gluconate and carbonate salts) daily in 2 doses  n=61 | | -- | -- | | -- | | -- | | | 1ǁǁǁǁ |
| Salovaara et al, 2010[106](#_ENREF_106)  Poor  Total n=3,195 | | 3 | ARD\*, 0.14% (95% CI, -0.51% to 0.78%)  RR, 1.17 (95% CI, 0.56 to 2.45) | | NR | | NR | | | NR |
| Control (no placebo)  n=1,609 | | -- | 13 (0.8) | | -- | | -- | | | -- |
| Vitamin D3 800 IU daily plus calcium 1,000 mg (as carbonate salt) daily in 2 divided doses  n=1,586 | | -- | 15 (0.9) | | -- | | -- | | | -- |
| Sanders et al, 2010[83](#_ENREF_83)  Good for all-cause mortality;Fair for incident CVD and incident cancer  Total N=2,258 randomized (N=2,256 analyzed) | | Median 3 | ARD\*, -0.64% (95% CI, -2.23% to 0.95%)  RR\*, 0.85 (95% CI, 0.56 to 1.28) | | ARD\*, 0.35% (95% CI, -0.60% to 1.29%)  RR\*, 1.30 (95% CI, 0.63 to 2.67) | | ARD\*, -0.27% (95% CI,  -0.98% to 0.44%)  RR\*, 0.70 (95% CI, 0.27 to 1.82) | | | NR |
| Placebo  n=1,125 | | -- | 47 (4.2) | | 13 (1.2) | | 10 (0.9) | | | -- |
| Vitamin D3 500,000 IU orally annually  n=1131 | | -- | 40 (3.5) | | 17 (1.5) | | 7 (0.6) | | | -- |
| Zhu et al, 2008[109](#_ENREF_109)  Fair  Total N=120 | | 5 | NR | | Stroke¶¶¶¶:  ARD\*, -2.38% (95% CI, -10.56% to 5.80%); RR\*, 0.51 (95% CI, 0.05 to 5.43) for calcium vs. placebo  ARD\*, -4.88% (95% CI, -12.82% to 3.06%); RR\*, 0.21 (95% CI, 0.01 to 4.24) for vitamin D with calcium vs. placebo  Ischemic heart disease¶¶¶¶:  ARD\*, 2.62% (95% CI, -7.87% to 13.11%); RR\*, 1.54 (95% CI, 0.27 to 8.72) for calcium vs. placebo  ARD\*, -4.88% (95% CI, -12.82% to 3.06%); RR\*, 0.21 (95% CI, 0.01 to 4.24) for vitamin D with calcium vs. placebo | | Cancer Including skin¶¶¶¶:  ARD\*, 5.55% (95% CI,  -13.21% to 24.31%); RR\*, 1.25 (95% CI, 0.58 to 2.69) for calcium vs. placebo  ARD\*, -6.57% (95% CI, -23.56% to 10.43%); RR\*, 0.70 (95% CI, 0.28 to 1.79) for vitamin D with calcium vs. placebo  Cancer excluding skin¶¶¶¶:  ARD\*, 5.43% (95% CI, -11.90% to 22.75%); RR\*, 1.32 (95% CI, 0.54 to 3.20) for calcium vs. placebo  ARD\*, -9.38% (95% CI,  -23.61% to 4.85%); RR\*, 0.45 (95% CI, 0.13 to 1.62) for vitamin D with calcium vs. placebo | | | No events in any study group |
| Placebo  n=41 | | -- | -- | | Stroke: 2 (5.0)  Ischemic heart disease: 2 (5.0) | | Cancer including skin: 9 (22.0)  Cancer excluding skin: 7 (17.1) | | | 0 (0) |
| Calcium 1,200 mg (as carbonate salt) daily  n=40 | | -- | -- | | Stroke: 1 (2.5)  Ischemic heart disease: 3 (7.5) | | Cancer including skin: 11 (27.5)  Cancer excluding skin: 9 (22.5) | | | 0 (0) |
| Calcium 1,200 mg (as carbonate salt) plus vitamin D2 1,000 IU orally daily  n=39 | | -- | -- | | Stroke: 0 (0)  Ischemic heart disease: 0 (0) | | Cancer including skin: 6 (15.4)  Cancer excluding skin: 3 (7.7) | | | 0 (0) |

\*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 the 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 (so were ages 52 to 61 at time of recruitment into the trial). 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. Five women were not included in the analysis because they were withdrawn after randomization due to osteoporosis (1 in placebo group and 4 in intervention group).

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

§ Study reported two cancer outcomes: Year 1 through Year 4, and Year 2 through Year 4 based on the hypothesis that Year 1 cancer outcomes are likely undetected prevalent cancers at baseline. ARD -3.2% (95% CI, -6.7% to 0.4%) and RR 0.53 (95% CI, 0.27 to 1.04) for calcium compared to placebo when cancers that occurred during the first year of followup were excluded. ARD, -4.8% (95% CI, -8.1% to -1.5%) and RR, 0.29 (95% CI, 0.13 to 0.67) for vitamin D with calcium compared to placebo when cancers that occurred during the first year of followup were excluded.

ǁ Analysis based on 290 participants who reported taking tablets at the end of the study (99 participants analyzed in placebo group, 98 in 600 mg calcium group, and 93 in 1,200 mg calcium group).

¶ Age-adjusted estimate for men was 1.11 (95% CI, 0.87 to 1.42), estimate for women 0.95 (95% CI, 0.54 to 1.68).

# Age-adjusted estimate for men was 1.17 (95% CI, 0.89 to 1.54), estimate for women 0.77 (95% CI, 0.39 to 1.55).

\*\* Age-adjusted estimate for men was 1.18 (95% CI, 0.65 to 2.12), estimate for women was 0.49 (95% CI, 0.12 to 1.98).

†† Age-adjusted estimate for men was 1.29 (95% CI, 0.62 to 2.68), estimate for women was NR because no cases occurred among the treatment group.

ǂǂ Results based on data provided across 12 WHI CaD trial publications Jackson et al, 2006[70](#_ENREF_70); Wactawski-Wende et al, 2006[112](#_ENREF_112); LaCroix et al, 2009[111](#_ENREF_111); Bolland et al, 2011[115](#_ENREF_115); Bolland et al, 2011[96](#_ENREF_96); Brunner et al, 2011[121](#_ENREF_121); Tang et al, 2011[120](#_ENREF_120); Wallace et al, 2011[113](#_ENREF_113); Prentice et al, 2013[97](#_ENREF_97); Blondon et al, 2015[116](#_ENREF_116); Hsia et al, 2007[162](#_ENREF_162), and Donneyong et al, 2015.[117](#_ENREF_117)

§§ Subgroup analyses based on age, personal use of supplements at baseline, and race/ethnicity. HR for age less than 70 years was 0.89 (95% CI, 0.80 to 0.99) and for age greater than or equal to 70 years was 0.95 (95% CI, 0.80 to 1.12); P for interaction between age and treatment allocation=0.10.[111](#_ENREF_111) HR for participants with no personal supplement use at baseline (N=7,755 placebo, N=7,891 for CaD) reported in two different publications: HR 0.95 (95% CI, 0.81 to 1.11)[97](#_ENREF_97) and HR 0.94 (95% CI, 0.81 to 1.10, P for interaction=0.44).[96](#_ENREF_96) HR for participants with personal supplement use at baseline (N=10,351 placebo, N=10,285 CaD) was 0.88 (95% CI, 0.77 to 1.01).[96](#_ENREF_96) Among racial/ethnically defined subgroups p for interaction with treatment allocation=0.30; white HR 0.89 (95% CI, 0.80 to 0.99), black HR 0.91 (95% CI 0.67 to 1.23), Hispanic HR 2.28 (95% CI, 1.07 to 4.87), American Indian HR 0.84 (95% CI, 0.16 to 4.48), Asian/Pacific Islander 1.60 (95% CI, 0.75 to 3.43); other/unknown 0.90 (95% CI, 0.45 to 1.80).[111](#_ENREF_111)

ǁǁ Subgroup analyses based on participants who did not use personal supplements at baseline: HR 1.03 (95% CI, 0.93 to 1.13).[97](#_ENREF_97) Subgroup analyses reported by WHI CaD authors for myocardial infarction events, HR for nonusers was 1.11 (95% CI, 0.90 to 1.37).[97](#_ENREF_97)

¶¶ Subgroup analysis of clinical myocardial infarction events (excluding silent MI) using the WHI limited access dataset of 16,718 women (N=8,289 placebo, N=8,429 CaD) who did not use personal supplements at baseline and 19,564 women (N=9,817 placebo, N=9,747 CaD) who used personal supplements at baseline; reported HR for nonusers was 1.11 (95% CI, 0.90 to 1.37) and HR for users was 1.22 (95% CI, 1.00 to 1.5); P for interaction=0.04.[115](#_ENREF_115)

## Based on a subgroup of 15,302 women (n=7,584 placebo, n=7,718 CaD) who did not use personal supplements at baseline. Participants with no personal supplement use at baseline: HR 1.03 (95% CI, 0.85 to 1.25).[97](#_ENREF_97) and no use of personal vitamin D supplements at baseline (p for interaction =0.45).[162](#_ENREF_162) HR by age groups (50 to 59, 60 to 69, and 70 to 79) showed no significant differences and p for interaction=0.53.[162](#_ENREF_162)

\*\*\* Based on a subgroup analysis using the WHI limited access dataset of 16,718 women (n=8,289 placebo, n=8,429 CaD) who did not use personal supplements at baseline and 19,564 women (n=9,817 placebo, n=9,747 CaD) who used personal supplements at baseline.[115](#_ENREF_115) Participants with personal supplement use at baseline: HR, 0.83 (95% CI, 0.67 to 1.02), participants with no personal supplement use HR, 1.17 (95% CI, 0.95 to 1.44), P for interaction=0.02. A similar finding reported by WHI study authors in a different publication; HR for nonusers of any personal supplements at baseline 1.12 (95% CI, 0.90 to 1.39).[97](#_ENREF_97" \o "Prentice, 2013 #1215) and for nonuse of personal vitamin D supplements at baseline (p for interaction 0.12).

†††Based on 35,983 women who did not have a prior diagnosis of heart failure at baseline.[117](#_ENREF_117) Subgroups based on risk status defined using American College of Cardiology criteria and based on the presence of hypertension, diabetes mellitus, coronary heart disease, or cardiovascular disease: high risk HR 1.06 (95% CI, 0.90 to 1.24), low risk HR 0.63 (95% CI, 0.46 to 0.87)

ǂǂǂ Events for women on oral hormone therapy were considered secondary. If those events are considered idiopathic, the HR would have been 0.82 (95% CI, 0.64 to 1.06) (Blondon et al, 2015[116](#_ENREF_116)).

§§§ This is the HR reported in Jackson et al, 2003[95](#_ENREF_95) and Prentice et al, 2013[97](#_ENREF_97), a slightly different HR (0.98 (95% CI, 0.91 to 1.05) was reported in Wactawski-Wende et al, 2006.[112](#_ENREF_112)

ǁǁǁ Subgroups by age categories: 50–59 years HR 1.02 (95% CI, 0.63 to 1.66), 60–69 years HR 1.01 (95% CI, 0.74 to 1.38), 70–79 years HR 1.24 (95% CI, 0.83 to 1.84). Subgroups by race/ethnicity: white: HR 1.12 (95% CI, 0.88 to 1.42), black: HR 0.85 (95% CI, 0.40 to 1.79), Hispanic: HR 0.84 (95% CI, 0.22 to 3.24), Indian/Alaska Native; NR, Asian or Pacific Islander: NR, Unknown: NR. HR 0.98 (95% CI, 0.90 to 1.05) based on a subgroup of 34,670 women (n=17327 placebo, n=17,343 CaD) who did not have a prior history of invasive cancer at baseline.[121](#_ENREF_121) As reported in Bolland et al (2011).[96](#_ENREF_96) Based on a subgroup of 15,646 women (n=7,755 placebo, n=7891 for CaD) who did not use personal supplements at baseline and 20,636 (n=10,351 placebo; n=10,285 CaD) women who used personal supplements at baseline, participants with personal supplement use at baseline HR 1.06 (95% CI, 0.97 to 1.17) and participants with no personal supplement use at baseline HR 0.86 (95% CI, 0.78 to 0.96); p for interaction=0.003).[96](#_ENREF_96) As reported in Wactawski-Wende et al (2006)[112](#_ENREF_112), participants with no personal supplement use at baseline HR 0.88 (95% CI, 0.78 to 0.98).

¶¶¶ Based on a subgroup of 15,646 women (n=7,755 placebo, n=7,891 for CaD) who did not use personal supplements at baseline and 20,636 women (n=10,351 placebo, n=10,285 CaD) who used personal supplements at baseline.[96](#_ENREF_96), [112](#_ENREF_112) As reported in Bolland et al (2011)[96](#_ENREF_96), participants with no personal supplement use at baseline HR 0.80 (95% CI, 0.66 to 0.96), participants with personal supplement use at baseline HR 1.12 (95% CI, 0.96 to 1.31), p for interaction=0.005. As reported in Wactawski-Wende et al (2006)[112](#_ENREF_112), participants with no personal supplement use at baseline HR 0.80 (95% CI, 0.66 to 0.96).

### As reported in Jackson et al, 2003[95](#_ENREF_95) and Prentice et al, 2013.[97](#_ENREF_97) Wactawski-Wende et al report a slightly different estimate, HR 1.08 (95% CI, 0.86 to 1.34).[112](#_ENREF_112)

\*\*\*\* Based on a subgroup of 15,646 women (n=7,755 placebo, n=7,891 for CaD) who did not use personal supplements at baseline and 20,636 women (n=10,351 placebo, n=10,285 CaD) who used personal supplements at baseline.[96](#_ENREF_96), [112](#_ENREF_112) As reported in Bolland et al[96](#_ENREF_96) participants with no personal supplement use at baseline HR 0.83 (95% CI, 0.60 to 1.15), participants with personal supplement use at baseline HR 1.26 (95% CI, 0.94 to 1.69), p for interaction=0.044. As reported in Wactawski-Wende et al (2006)[112](#_ENREF_112), participants with no personal supplement use at baseline HR 0.80 (95% CI, 0.66 to 0.96).

†††† Participants with no history of nonmelanoma skin cancer HR 1.02 (95% CI, 0.95 to 1.07), participants with history of nonmelanoma skin cancer HR 0.43 (95% CI, 0.21 to 0.90).[120](#_ENREF_120" \o "Tang, 2011 #1353)

‡‡‡‡As reported by Wactawski-Wende et al, 2006[112](#_ENREF_112) and Wallace et al, 2011.[113](#_ENREF_113) Subgroups by age (P for interaction=0.194): 50–59 years HR 1.06 (95% CI, 0.84 to 1.33), 60–69 years HR 1.34 (95% CI, 1.10 to 1.63), 70–79 years HR 0.99 (95% CI, 0.72 to 1.38). Subgroups by race (P for interaction 0.806): white HR 1.21 (95% CI, 1.04 to 1.41), black HR 1.10 (95% CI, 0.71 to 1.71), Hispanic HR 0.90 (95% CI, 0.50 to 1.62), American Indian HR 0.84 (95% CI, 0.20 to 3.61), Asian/Pacific Islander HR 1.24 (95% CI, 0.49 to 3.17).

§§§§ 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

ǁǁǁǁ Kidney stones were reported as a reason for dropout and not necessarily a specific harm.

¶¶¶¶ Based on supplemental data supplied by the author.

**Abbreviations:** ADE=adverse drug events; ARD=absolute risk difference; CI=confidence interval; CVD=cardiovascular disease; ITT=intent to treat; MI=myocardial infarction; NR=not reported; RR=relative risk; SAE=serious adverse event; VTE=venous thromboembolism; WHI CaD=Women’s Health Initiative Calcium and Vitamin D Trial; WHO GCP=World Health Organization Good Clinical Practice.