| **Author, Year**  **Trial Name, No. of Participants** | **Other Harms Reported\*** |
| --- | --- |
| Aloia et al, 2005[114](#_ENREF_114)  Total N=208 | AE total: 222  SAE (none were thought to be related to the study):  Vitamin D with calcium group: 8  Calcium group: 7 |
| Cherniack et al, 2011[119](#_ENREF_119)  Total N=46 | No significant differences in adverse events between treatment and control groups, and all were considered unrelated to supplementation.  AE resulting in withdrawal:  Vitamin D group: 3 (ankle swelling, bradycardia due to sick sinus syndrome, MI)  Placebo group: 4 (breast tenderness, cellulitis, atrial fibrillation, MI)  AE not resulting in withdrawal:  Vitamin D group: 1(diarrhea)  Placebo group: 1 (neck pain and chills) |
| Dawson-Hughes et al, 1997[74](#_ENREF_74)  Total N=445 | Discontinuations due to side effects: 9  Vitamin D with calcium group: 6 (3 constipation, 1 epigastric distress, 1 sweating, 1 hyper calciuria)  Placebo group: 3 (2 epigastric distress, 1 flank pain) |
| Glendenning et al, 2012[86](#_ENREF_86)  Total N=686 | Incident type 2 DM:  Vitamin D group: 0.3%  Placebo group: 0.5% |
| Hin et al, 2007[110](#_ENREF_110)  Total N=305 | Serious AEs:  Vitamin D 4,000 IU/d: 2.8%  Vitamin D 2,000 IU/d: 2.9%  Placebo: 2.5%  None were considered treatment-related. |
| Komulainen et al, 1998,[71](#_ENREF_71) Komulainen et al, 1999[118](#_ENREF_118)  Osteoporosis Risk Factor and Prevention Study#  Total N=232 | Serious AEs:  Vitamin D group: 1 (endometrial hyperplasia)  Placebo group: 1 (endometrial hyperplasia) |
| Lappe et al, 2007[107](#_ENREF_107)  Total N=1,180†† | No SAEs were reported.  “No patterns of adverse events were seen among the 3 groups.” |
| Lips et al, 1996[75](#_ENREF_75)  Total N=2,578 | NR |
| Peacock et al, 2000[85](#_ENREF_85)  Total N=438 randomized (N=393 with baseline values, N= 282 analyzed) | Gastrointestinal distress (mainly constipation) resulting in withdrawal: 12  Vitamin D group: NR  Calcium group: 10  Placebo: NR |
| Prince et al, 2006,[89](#_ENREF_89)and Lewis et al, 2011[90](#_ENREF_90) and Zhu et al, 2008[109](#_ENREF_109)  Calcium Intake Fracture Outcome Study  Total N=1,460 | Total number of AE recorded: 92,000  Constipation was the only AE higher in the treatment group compared with placebo group.  Calcium group: 13.4%  Placebo group: 9.1%  No difference in the number of participants who withdrew due to constipation. |
| Recker et al, 1996[72](#_ENREF_72)  Total N=103 (subgroup of overall participants) | Constipation (did not require study withdrawal)  Calcium group: 7  Placebo group: 1 |
| Reid et al, 2006,[87](#_ENREF_87)  Bolland et al, 2008[88](#_ENREF_88)  Total N=1,471 | Constipation:  Calcium group: 132 (18%)  Placebo: 82 (11%)  p=0.0002  Discontinuation of study treatment:  Calcium group: 336  Placebo group: 296  p=0.02  Health reasons more often cited as reason for discontinuation in calcium group (n=133) compared with placebo (n=105), p=0.04, and was mostly attributed to constipation. |
| Reid et al, 1995,[92](#_ENREF_92) Reid et al, 1993[94](#_ENREF_94)  Total N=135 randomized; N=122 completed initial trial | Withdrawals due to illness: 6  Of those, 4 were determined to be unrelated to study treatment:  nasopharyngeal carcinoma, thyrotoxicosis, rheumatoid arthritis, chronic lymphatic leukemia  Of the remaining 2 withdrawals:  Calcium group: 1 (kidney stone)  Placebo group: 1 dyspepsia |
| Reid et al, 2008[91](#_ENREF_91)  Total N=323 | AE:  Calcium 600 mg group: 69%  Calcium 1,200 mg group: 70%  Placebo group: 75%  p=0.16  No significant differences in protocol-specified AEs including transient ischemic attack or constipation. |
| Riggs et al, 1998[73](#_ENREF_73)  Total N=236 | Discontinuations due to side effects: 16  Calcium group: 10  Placebo group: 6  Excessive gastrointestinal symptoms (abdominal cramping, constipation, bloating, diarrhea)  Calcium group: 9  Placebo group: 2  Arthralgia and depression: Calcium group: 0  Placebo group: 1 |
| Ruml et al, 1999[93](#_ENREF_93)  Total N=63 | NR |
| Salovaara et al, 2010[106](#_ENREF_106)  Total N=3,432 | Discontinuation due to adverse effects:113  Gastrointestinal symptoms: 64  Nausea: 12  Skin reactions: 9 |
| Sanders et al, 2010[83](#_ENREF_83)  Total N=2,258 randomized (N=2,256 analyzed) | Number of participants reporting at least one AE:  Vitamin D group: 19.7%  Placebo group: 17.8%  SAE (defined as events requiring hospitalization or death):  Vitamin D group: 244  Placebo group: 207  p=0.06  None of the SAEs were considered related to study medication. |
| Smith et al, 2007[84](#_ENREF_84)  Total N=9,440 | NR |
| Trivedi et al, 2003[76](#_ENREF_76)  Total N=2,686 | NR |
| WHI Calcium and Vitamin D Trial  Total N=36,282 | No significant differences in gastrointestinal symptoms:  Moderate to severe constipation:  Vitamin D with calcium group: 10.3%  Placebo group: 8.9%  Bloating or gas:  Vitamin D with calcium group: 20.4%  Placebo group: 19.5% |

\* Includes outcomes other than all-cause mortality, kidney stones, incident cardiovascular disease and incident cancer, which are reported in Appendix D Table 3.

**Abbreviations:** AE=adverse events; NR=not reported; SAE=serious adverse events; WHI CaD=Women’s Health Initiative.