| **Author, Year, Title** | **Population Characteristics** | **Eligibility Criteria** | **Assay** | **Definition of Deficiency/ Insufficiency** | **Baseline 25(OH)D Level (ng/mL)** | **25(OH)D Level**  **Attained (ng/mL)** |
| --- | --- | --- | --- | --- | --- | --- |
| Overall WHI Trial Fair | Mean age (years): 62\* Female: 100% Race: 83.1% white; 9.1% black; 4.2% Hispanic; 0.42% American Indian or Native American; 2.0% Asian or Pacific Islander; 1.2% unknown or not identified Mean BMI (kg/m2): 29  History of fracture at any age: 35%  Number of women with falls in last 12 months: 67% with no falls, 20% with 1 fall, 9% with 2 falls, 4% with >3 falls | Inclusion: Postmenopausal women in the WHI hormone therapy and dietary modification trials ages 50 to 70 years with predicted survival of >3 years and no safety, adherence, or retention risks. Exclusion: History of hypercalcemia, kidney stones; current use of corticosteroids, calcitriol, and ≥600 IU/day of vitamin D. | Chemiluminescent immunoassay | NR | NR | NR for all participants; after 2 years, in subsample (selected without regard to nonstudy supplement use or adherence to medication) of 227 women assigned to vitamin D and 221 women assigned to placebo, vitamin D levels were 28% higher (9 ng/mL) in women taking vitamin D |
| Jackson et al, 2006164 *Calcium plus vitamin D supplementation and the risk of fractures* | Number of cases (annualized %) of hip fracture in vitamin  D vs. control by baseline characteristics Age group at screening (years);HR all NS 50 to 59: 29 (0.06) vs. 13 (0.03) 60 to 69: 53 (0.09) vs. 71 (0.13) 70 to 79: 93 (0.44) vs. 115 (0.54) Race or ethnic group;HR all NS White: 167 (0.16) vs. 189 (0.18) Black: 3 (0.03) vs. 4 (0.04) Hispanic: 0 (0) vs. 3 (0.06) American Indian: 1 (0.19) vs. 1 (0.20) Asian or Pacific Islander: 4 (0.16) vs. 1 (0.04) Unknown or not identified: 0 (0) vs. 1 (0.07) | Cases: All adjudicated cases of hip, spine, and lower arm or wrist fracture. Controls: Free of fracture for the duration of study; individually matched to cases by age, latitude of clinical center, race or ethnic group, and date of venipuncture. | As above | NR | 90% <31; outcomes presented in quartiles of baseline 25(OH)D level as >24, 18 to 24, 13 to 18, and <13 ng/mL | As above |
| Wactawski-Wende et al, 2006168 *Calcium plus vitamin D supplementation and the risk of colorectal cancer* | Number of cases (annualized %) of invasive colorectal cancer in vitamin D vs.  control by baseline characteristics Age group at screening (years); HR all NS 50 to 59: 33 (0.07) vs. 32 (0.07) 60 to 69: 81 (0.14) vs. 78 (0.14) 70 to 79: 54 (0.25) vs. 44 (0.21) Race or ethnic group;HR all NS White: 145 (0.14) vs. 129 (0.12) Black: 13 (0.11) vs. 16 (0.14) Hispanic: 5 (0.09) vs. 4 (0.08) American Indian/Alaskan Native: 2 (0.37) vs. 0 (0) Asian or Pacific Islander: 2 (0.08) vs. 3 (0.13) Unknown or not identified: 1 (0.07) vs. 2 (0.13) | Cases: Women with confirmed invasive colorectal cancer and adequate stored serum for analysis. Controls: Women free of colorectal cancer for the duration of study with adequate stored serum for analysis; individually matched to cases according to age, latitude of clinical center, race or ethnic group, and date of venipuncture. | As above | NR | NR; outcomes presented in quartiles of baseline 25(OH)D level as ≥23, 17 to 23, 12 to 17, and <12 ng/mL | As above |
| Chlebowski et al, 2008167 *Calcium plus vitamin D supplementation and the risk of breast cancer* | Number of cases (annualized %) of invasive breast cancer in vitamin D vs. control by baseline characteristics Age group at screening (years); HR all NS 50 to 59: 179 (0.36) vs. 196 (0.40) 60 to 69: 247 (0.43) vs. 257 (0.45) 70 to 79: 102 (0.48) vs. 93 (0.44) | Cases: Women diagnosed with invasive breast cancer. Controls: Women who were breast cancer free; matched to cases on age, latitude of clinical center, race/ethnicity, date of blood collection. | As above | NR | NR; outcomes presented in quintiles of baseline 25(OH)D level as ≥27, 22 to 27, 18 to 22, 13 to 18, and <13 ng/mL | As above |
| de Boer et al, 2008169 *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative* | Number of cases (annualized %) of incident diabetes in vitamin D vs. control by baseline characteristics Age group at screening (years);HR all NS 50 to 59: 431 (0.91) vs. 426 (0.91) 60 to 69: 535 (1.01) vs. 518 (0.98) 70 to 79: 188 (0.95) vs. 193 (0.98) Race/ethnic group; HR=NS White: 846 (0.84) vs. 855 (0.85) Black: 166 (1.66) vs. 163 (1.66) Hispanic: 89 (1.81) vs. 71 (1.57) American Indian: 4 (0.87) vs. 5 (1.05) Asian or Pacific Islander: 32 (1.41) vs. 24 (1.13) Unknown: 17 (1.29) vs. 19 (1.37) | Cases and controls: Women with prevalent diabetes at baseline were excluded; selected from controls used in case-control study of fracture (Jackson 2008), in which participants were free of fracture for the duration of study and were individually matched to fracture cases by age, latitude of clinical center, race or ethnic group, and date of venipuncture. Cases: Women with new physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin. Controls: Women with no physician diagnosis of diabetes treated with oral hypoglycemic agents or insulin. | As above | NR | <32 for 89% of participants; <20 for 61% of participants; outcomes presented in quartiles of baseline 25(OH)D level as >24, 17 to 24, 13 to 17, and <13 ng/mL | As above |
| LaCroix et al, 2009152 *Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial* | Number of cases (annualized %) of death in vitamin D vs. control by baseline characteristics Race/ethnic group; HR=NS, except where noted White: 607 (0.57) vs. 679 (0.64); HR, 0.89 (95% CI, 0.80 to 0.99) Black: 79 (0.68) vs. 89 (0.78) Hispanic: 23 (0.42) vs. 11 (0.22); HR, 2.28 (95% CI, 1.07 to 4.87) American Indian: 5 (0.93) vs. 4 (0.79) Asian or Pacific Islander: 18 (0.73) vs. 12 (0.51) Unknown: 12 (0.83) vs. 12 (0.81) | Cases: Women who died and had baseline vitamin D levels from their involvement in previous WHI case-control studies of fracture and colorectal cancer (Jackson 2008; Wactawski-Wende 2006). Controls: Living participants from previous WHI case-control studies of fracture and colorectal cancer (Jackson 2008; Wactawski-Wende 2006). | As above | NR | NR; outcomes presented in tertiles of baseline 25(OH)D level as ≥21, 14 to 21, and <14 ng/mL | As above |

| **Author, Year, Title** | **Number Approached, Screened, Eligible,**  **Enrolled, Analyzed** | **Country and**  **Setting** | **UV Exposure** | **Duration of Followup** | **Attrition** |
| --- | --- | --- | --- | --- | --- |
| Overall WHI Trial Fair | Approached: 68,132  Screened: 68,132 Eligible: 36,282 | Multicenter U.S. population-based Institutionalized: NR | Solar irradiance of region for entire trial (Langley): Mean, 382±60 (controls matched to cases on this parameter) | Mean, 7.0 years  (SD, 1.4) | Overall: 7.0% (2531/ 36,282) Vitamin D vs. control: 6.8% (1240/18,176) vs. 7.1% (1291/18,106) |
| Jackson et al, 2006164 *Calcium plus vitamin D supplementation and the risk of fractures* | Enrolled: 1067 cases, 1067 controls, 357 pairs for hip fracture, 1491 pairs for total fracture in case-control study† Analyzed: 357 (95%) pairs for hip fracture, 1491 (80%) pairs for total fracture in case-control study | As above | Number of cases (annualized %) of hip fracture in vitamin D3 vs. control by solar irradiance (Langley); HR=NS 300 to 325: 46 (0.12) vs. 53 (0.14)  350: 37 (0.14) vs. 49 (0.18) 375 to 380: 25 (0.18) vs. 17 (0.12) 400 to 430: 25 (0.12) vs. 37 (0.17) 475 to 500: 42 (0.16) vs. 43 (0.16) | As above | As above |
| Wactawski-Wende  et al, 2006168 *Calcium plus vitamin D supplementation and the risk of colorectal cancer* | Eligible: 322  Enrolled: 634 (317 pairs for case-control study) Analyzed: 612 (306 [96.5%] pairs for case-control study) | As above | As above | As above | As above |
| Chlebowski et al, 2008167 *Calcium plus vitamin D supplementation and the risk of breast cancer* | Eligible: 1074 Enrolled: 1067 cases, 1067 controls Analyzed: 895 cases, 895 controls | As above | As above | As above | As above |
| de Boer et al, 2008169 *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative* | Eligible: 1699 controls from previous case-control study (Jackson 2008)‡ Analyzed: 3097 | As above | Vitamin D vs. control Number of events/at risk (annualized %) by solar irradiance of region (Langley); HR=NS 400 to 500: 459/6455 (1.02) vs. 435/6431 (0.97) 350 to 380: 414/5475 (1.08) vs. 423/5467 (1.10) 300 to 325: 281/5069 (0.77) vs. 279/5054 (0.77) | As above | As above |
| LaCroix et al, 2009152 *Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial* | Eligible: 3594 (2982 from fracture case-control study, 612 from colorectal case-control study) Enrolled: 2285 (323 cases, 1962 controls) Analyzed: 2285 (323 cases, 1962 controls) | As above | As above | As above | As above |

| **Author, Year, Title** | **Interventions** | **Calcium and Other Nutrients** | **Determination of Outcomes** | **Clinical Health Outcomes: Vitamin D vs. Control** | **Sponsor** |
| --- | --- | --- | --- | --- | --- |
| Overall WHI Trial Fair | Vitamin D: 200 IU of vitamin D3 BID (total, 400 IU/day) + 500 mg  of calcium carbonate BID (total, 1000 mg/day) Control: Identical placebo BID | Personal use of ≤1000 mg/day calcium and ≤600 IU/day vitamin D allowed. Vitamin D allowance increased to ≤1000 IU/day during trial. At baseline, 39% of participants had intake ≥1200 mg and 43% were using ≥400 IU/day vitamin D. At year 6, nonprotocol vitamin D use reported by 52% of participants and nonprotocol calcium intake increased by about 100 mg/day in both groups. | See individual studies below | See individual studies below | National Institutes of Health |
| Jackson et al, 2006164 *Calcium plus vitamin D supplementation and the risk of fractures* | As above | As above | Fractures: Verified by review of radiology, magnetic resonance imaging, or operative reports by blinded physician adjudicators at each clinical center. Final adjudication of hip fractures performed centrally. | Incidence and risk for hip fracture (number of cases/controls) by baseline vitamin D level (ng/mL) ≥24: 32/49 vs. 42/40; OR, 0.61 (95% CI, 0.32 to 1.15) 18 to 24: 44/40 vs. 52/39; OR, 0.86 (95% CI, 0.48 to 1.15) 13 to 18: 43/48 vs. 48/49; OR, 0.92 (95% CI, 0.53 to 1.62) <13: 47/44 vs. 49/48; OR, 1.06 (95% CI, 0.60 to 1.86) p=0.64 for interaction Incidence and risk for total fracture (number of cases/controls) by baseline vitamin D level (ng/mL) ≥24: 178/185 vs. 177/201; OR, 1.09 (95% CI, 0.81 to 1.47) 18 to 24: 170/179 vs. 205/191; OR, 0.89 (95% CI, 0.66 to 1.18) 13 to 18: 179/183 vs. 204/181; OR, 0.87 (95% CI, 0.66 to 1.16) <13: 196/167 vs. 182/204; OR, 1.32 (95% CI, 0.99 to 1.76) p=0.15 for interaction | National Heart, Lung, and Blood Institute; General Clinical Research Center Program of the National Center for Research Resources; several investigators supported by industry |
| Wactawski-Wende et al, 2006168 *Calcium plus vitamin D supplementation and the risk of colorectal cancer* | As above | As above | Invasive colorectal cancer: reported cases verified in a blinded fashion by local and central physician adjudicators. Tests for colorectal cancer screening were not part of the protocol and were ordered by each participant’s personal physician. | Incidence and risk for colorectal cancer (number cases/controls) by baseline vitamin D level (ng/mL) ≥23: 33/48 vs. 27/45; OR, 1.15 (95% CI, 0.58 to 2.27)  17 to 23: 44/41 vs. 34/32; OR, 1.12 (95% CI, 0.59 to 2.12) 12 to 23: 35/32 vs. 45/41; OR, 0.99 (95% CI, 0.51 to 1.91)  <12.4: 46/39 vs. 42/28; OR, 0.75 (95% CI, 0.39 to 1.48)  p=0.54 for interaction | National Heart, Lung, and Blood Institute General Clinical Research Center Program  of the National Center for Research Resources; several investigators supported by industry |
| Chlebowski et al, 2008167 *Calcium plus vitamin D supplementation and the risk of breast cancer* | As above | As above | Invasive breast cancer: Confirmed by both local and central medical record and pathology report review by trained adjudicators who were blinded to group allocation. | Incidence and risk for invasive breast cancer (number of cases/controls) by baseline vitamin D level (ng/mL) ≥27: 86/109 vs. 76/86; aOR, 0.89 (95% CI, 0.58 to 1.36) 22 to 27: 95/87 vs. 86/98; aOR, 1.25 (95% CI, 0.83 to 1.90) 18 to 22: 102/87 vs. 92/84; aOR, 1.07 (95% CI, 0.70 to 1.62) 13 to 18: 71/84 vs. 102/87; aOR, 0.69 (95% CI, 0.45 to 1.06) <13: 94/94 vs. 91/82; aOR, 0.91 (95% CI, 0.60 to 1.39) p≥0.99 for interaction aOR=adjusted for age, race, latitude, venipuncture date, randomization in hormone therapy and dietary modification trials, BMI, physical activity, family history of breast cancer, history of breast biopsy, and current hormone therapy use | National Heart, Lung, and Blood Institute; one author supported by industry |
| de Boer et al, 2008169 *Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative* | As above | As above | Diabetes: Case-identification by self-report of a doctor prescribing medication or insulin for diabetes. Study states that accuracy of self- reported treated diabetes in WHI previously assessed using medication and laboratory data. | Incidence and risk for diabetes (number of events/at-risk) by baseline vitamin D level (ng/mL) ≥24: 20/395 vs. 24/397; OR, 0.62 (95% CI, 0.32 to 1.20)  17 to 24: 22/366 vs. 16/402; OR, 1.60 (95% CI, 0.80 to 3.18) 13 to 17: 17/371 vs. 30/394; OR, 0.66 (95% CI, 0.36 to 1.23) <13: 30/381 vs. 33/391; OR, 1.07 (95% CI, 0.62 to 1.82) p=0.59 for interaction | National Heart, Lung, and Blood Institute; National Institutes of Health Roadmap for Medical Research |
| LaCroix et al, 2009152 *Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial* | As above | As above | Mortality: For women who could not be contacted, information about vital status was sought from previously identified proxy informants, National Death Index searches, and obituary notices. Causes of death were determined based on available medical records, autopsy reports, and the death certificate in a blinded fashion by local and central physician adjudicators. | Incidence and risk for death (number of cases/controls) by baseline vitamin D level (ng/mL) ≥21: 53/404 vs. 50/425; aOR, 1.04 (95% CI, 0.69 to 1.59) 14 to 21: 57/301 vs. 59/296; aOR, 0.96 (95% CI, 0.64 to 1.45) <14: 47/270 vs. 57/266; aOR, 0.79 (95% CI, 0.51 to 1.23) p=0.65 for interaction aOR=stratified by age group, randomization to hormone therapy or diet modification and adjusted for age, ethnicity, latitude of clinical center, season of blood draw, and treatment assignment | National Heart, Lung, and Blood Institute |

\* Population characteristics are of all WHI trial participants (n=36,282), not the subgroup with serum vitamin D levels.

† Text states 357 case-control pairs included for hip fracture and 1491 pairs included for total fracture, which is less than the sum of numbers noted above for eligible fractures; unclear why these numbers do not match.

‡ Discrepancy between the number of controls enrolled as cited in this case-control study (n=1699) and the number that were eligible from previous case-control study based on that study's publication (n=1491); unclear how the number analyzed was computed.

**Abbreviations:** aOR = adjusted odds ratio; BMI = body mass index; BID = twice a day; CI = confidence interval; HR = hazard ratio; NR = not reported; NS = not significant; OR = odds ratio; SD = standard deviation; UV = ultraviolet; WHI = Women's Health Initiative.