Supplemental Table 1. Candidate covariates that were tested in the models

|  |  |
| --- | --- |
| Variables | Categories |
| Demographic factors |  |
| Age | Continuous |
| Sex | Male, female |
| Hispanic ethnicity | No, yes |
| Race | White, Black, Asian/Pacific Islander, Other/unknown/refused |
| Education | Did not graduate high school, Graduated high school, Any college education |
| Year of baseline blood draw | 2004, 2005, 2006, 2007, 2008 |
| Sun-related factors |  |
| Season of baseline blood draw | December-February, March-May, June-August, September-November |
| Latitude of study center | Northern 43-450, 35-420, Southern <350 |
| Artificial tanning | No, Yes |
| Sunscreen use | Never-rarely (0-10%), Sometimes (11-85%), Almost Always (86-100%) |
| Number of vacation days in a sunny location | None, 1-7, 8-14, 15-120 |
| Wears pants / sleeves in 3 month period when outside most | Never, rarely (0-10%), Sometimes (11-50%), Usually (51-85%), Almost Always (86-100%) |
| Behavioral factors |  |
| Body mass index | <25, 25-29, 30-34, ≥35 |
| Smoking status | Never, former, current |
| Alcohol intake | <=1, 1.1-13.5, 13.6-30, >30 grams /day |
| Activity level | Low, moderate, high |
| Health-related factors |  |
| Ever had hypertension | No, Yes |
| Ever had high cholesterol | No, Yes |
| Fracture in the last 5 years | No, Yes |
| Menopausal status | Pre, post |
| Number of live births | 0, ≥1 |
| Medications |  |
| Diabetes | Not diabetic, Insulin dependent, Non-insulin dependent, Diet controlled |
| Gout | No, History but no current preventive treatment, Current prevention treatment |
| Protein pump inhibitor1 | No, Yes |
| H2 blocker1 | No, Yes |
| Any cholesterol lowering drug1 | No, Yes |
| Statin1 | No, Yes |
| Anticonvulsant1 | No, Yes |
| Calcium channel blocker1 | No, Yes |
| Diuretic1 | None, 1, 2 or more |
| Warfarin1 | No, Yes |
| Oral corticosteroid1 | No, Yes |
| Hormone replacement | Never, former, current |
| Health-related factors |  |
| Ever had hypertension | No, Yes |
| Ever had high cholesterol | No, Yes |
| Fracture in the last 5 years | No, Yes |
| Diabetes | Not diabetic, Insulin dependent, Non-insulin dependent, Diet controlled |
| Gout | No, History but no current preventive treatment, Current prevention treatment |
| Menopausal status | Pre, post |
| Number of live births | 0, ≥1 |
| Medications |  |
| Protein pump inhibitor1 | No, Yes |
| H2blocker1 | No, Yes |
| Any cholesterol lowering drug1 | No, Yes |
| Statin1 | No, Yes |
| Anticonvulsant1 | No, Yes |
| Calcium channel blocker1 | No, Yes |
| Diuretic1 | No, Yes |
| Warfarin1 | No, Yes |
| Oral steroid1 | No, Yes |
| Hormone replacement | Never, former, current |
| Nutritional factors |  |
| Calcium randomization group2 | 1200mg calcium carbonate daily or placebo |
| Personal supplemental calcium1 | None, 1-200mg, >200mg, Unknown amount |
| Dietary calcium | Sex specific quartiles |
| Personal supplemental vitamin D1 | None, 1-399IU, ≥400IU, Unknown amount |
| Dietary vitamin D | Sex specific quartiles |
| Dairy servings | Sex specific quartiles |
| Cod liver supplement1 | No, yes |
| Fish oil supplement1 | No, yes |
| Multivitamin1 | No, yes |
| Dietary zinc | Sex specific quartiles |
| Dietary magnesium | Sex specific quartiles |
| Genes | SNPs |
| *GC* (vitamin D-binding protein) | rs12512631, rs2282679, rs3755967, rs4588, rs7041, rs222020, rs16847015, rs1155563, rs2298849 |
| *DHCR7* (7-dehydrocholesterol reductase) | rs12785878, rs3829251 |
| *CYP2R1* (25-hydroxylase) | rs12794714, rs10741657, rs2060793, rs1562902, rs10766197 |
| *CYP27B1* (1-hydroxylase) | rs4646536, rs10877012, rs703842 |
| *CYP24A1* (24-hydroxylase) | rs6013897, rs2209314, rs2762939, rs4809958, rs2244719, rs2296241, rs17219315 | |
| *VDR* (vitamin D receptor) | rs7968585, rs11574143, rs731236, rs7975232, rs1544410, rs2239179, rs2228570, rs10783219, rs4516035, rs7139166, rs11568820 |
| *CASR* (calcium-sensing receptor) | rs17251221, rs1801725, rs1042636, rs1801726 |

1 Variables reflect status or use at baseline. For response models, these variables reflect use between randomization and Year 1.

2 Calcium was provided to all women in the 2-arm randomization; but was randomly allocated to men and women in the 4-arm randomization.

Supplemental Table 2. Associations between baseline medication use and 25-hydroxyvitamin D status

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | N (%) | 25(OH)D, ng/mL1 | Unadjusted  Estimate2  % (95% CI) | *P* | Adjusted  Estimate2  % (95% CI) | *P* | |
| Hormone replacement (women) |  |  |  | 0.001 |  | 0.004 | |
| Never | 548 (53) | 22.6 ± 8.3 | Reference |  | reference |  | |
| Former | 338 (33) | 23.6 ± 8.7 | 4.3 (-0.8, 9.6) |  | 0.8 (-3.3, 5.1) |  | |
| Current | 148 (14) | 26.0 ± 10.1 | 13.8 (6.5, 21.6) |  | 10.0 (3.9, 16.4) |  | |
|  |  |  |  |  |  |  | |
| Oral corticosteroids |  |  |  | 0.002 |  | 0.02 | |
| No | 2,718 (99) | 23.9 ± 8.6 | Reference |  | reference |  | |
| Yes | 35 (1.3) | 19.5 ± 5.8 | -16.8 (-26.0, -6.4) |  | -11.6 (-20.3, -2.0) |  | |
|  |  |  |  |  |  |  | |
| Calcium channel blocker |  |  |  | 0.72 |  | 0.02 | |
| No | 2,561 (93) | 23.9 ± 8.6 | reference |  | reference |  | |
| Yes | 192 (7.0) | 23.7 ± 8.6 | -1.0 (-6.0, 4.3) |  | 5.6 (0.8, 10.7) |  | |
|  |  |  |  |  |  |  | |
| Diabetes medications |  |  |  | <0.0001 |  | 0.37 | |
| No history | 2,471 (90) | 24.2 ± 8.7 | reference |  | reference |  | |
| Diet controlled | 60 (2.2) | 22.6 ± 8.0 | -6.7 (-14.7, 2.1) |  | 4.7 (-3.4, 13.6) |  | |
| Non insulin dependent | 182 (6.6) | 21.1 ± 7.2 | -12.5 (-17.0, -7.7) |  | -1.8 (-6.4, 3.1) |  | |
| Insulin-dependent | 37 (1.4) | 19.5 ± 6.2 | -18.7 (-27.5, -8.9) |  | -5.8 (-15.2, 4.5) |  | |
|  |  |  |  |  |  |  | |
| Diuretics |  |  |  | <0.0001 |  | 0.87 | |
| None | 2,243 (81) | 24.2 ± 8.7 | reference |  | reference |  | |
| 1 | 408 (15) | 22.6 ± 7.8 | -6.6 (-10.0, -3.1) |  | -0.5 (-3.8, 2.9) |  | |
| 2 or more | 102 (3.7) | 21.5 ± 8.4 | -12.4 (-18.3, -6.1) |  | -1.4 (-7.4, 4.9) |  | |
|  |  |  |  |  |  |  | |
| Thiazide |  |  |  | 0.0001 |  | 0.99 | |
| No | 2,281 (83) | 24.2 ± 8.7 | Reference |  | reference |  | |
| Yes | 472 (17) | 22.5 ± 7.9 | -6.9 (-10.1, -3.6) |  | 0.0 (-3.1, 3.2) |  | |
|  |  |  |  |  |  |  | |
| Loop |  |  |  | 0.002 |  | 0.15 | |
| No | 2,716 (99) | 23.9 ± 8.6 | Reference |  | reference |  | |
| Yes | 37 (1.3) | 20.1 ± 8.3 | -16.5 (-25.5, -6.4) |  | -7.0 (-15.7, 2.7) |  | |
|  |  |  |  |  |  |  | |
| Potassium-sparing |  |  |  | 0.001 |  | 0.68 | |
| No | 2,665 (97) | 24.0 ± 8.6 | Reference |  | Reference |  | |
| Yes | 88 (3.2) | 21.5 ± 8.9 | -11.8 (-18.2, -4.9) |  | -1.4 (-7.7, 5.4) |  | |
|  |  |  |  |  |  |  | |
| Anticonvulsants (excluding benzodiazepines): |  |  |  | 0.06 |  | 0.15 | |
| No | 2,700 (98) | 23.9 ± 8.6 | reference |  | reference |  | |
| Yes | 53 (1.9) | 21.7 ± 7.4 | -8.9 (-17.3, 0.3) |  | -6.1 (-13.8, 2.4) |  | |
|  |  |  |  |  |  |  | |
| Gabapentin |  |  |  | 0.05 |  | 0.54 | |
| No | 2,728 (99) | 23.9 ± 8.6 | reference |  | reference |  | |
| Yes | 25 (0.9) | 20.6 ± 6.9 | -13.2 (-24.5, -0.3) |  | -3.9 (-15.2, 9.0) |  | |
|  |  |  |  |  |  |  | |
| Proton pump inhibitors3 |  |  |  | 0.001 |  | 0.17 | |
| No | 2,375 (86) | 24.1 ± 8.7 | reference |  | reference |  | |
| Yes | 378 (14) | 22.7 ± 8.2 | -6.1 (-9.7, -2.5) |  | -2.3 (-5.6, 1.0) |  | |
|  |  |  |  |  |  |  | |
| H2 blockers3 |  |  |  | 0.98 |  | 0.43 | |
| No | 2,668 (97) | 23.9 ± 8.6 | Reference |  | reference |  | |
| Yes | 85 (3.1) | 23.8 ± 8.7 | -0.11 (-7.5, 7.8) |  | 2.7 (-3.9, 9.9) |  | |
|  |  |  |  |  |  |  | |
| Fish oil |  |  |  | 0.05 |  | 0.23 | |
| No | 2,678 (97) | 23.8 ± 8.6 | Reference |  | Reference |  | |
| Yes | 75 (2.7) | 25.8 ± 9.5 | 8.3 (-0.1, 17.5) |  | 4.3 (-2.6, 11.8) |  | |
|  |  |  |  |  |  |  | |
| Warfarin-like anticoagulants |  |  |  | 0.06 |  | 0.51 | |
| No | 2,724 (99) | 23.9 ± 8.6 | reference |  | reference |  | |
| Yes | 29 (1.1) | 20.8 ± 6.0 | -11.5 (-22.2, 0.7) |  | -3.8 (-14.1, 7.8) |  | |
|  |  |  |  |  |  |  | |
| Non statin cholesterol lowering drugs | |  |  | 0.46 |  | 0.77 |
| No | 2,619 (95) | 23.9 ± 8.6 | Reference |  | Reference |  | |
| Yes | 134 (4.9) | 23.2 ± 8.0 | -2.3 (-8.1, 3.9) |  | 0.8 (-4.6, 6.5) |  | |
|  |  |  |  |  |  |  | |
| Statins |  |  |  | 0.42 |  | 0.92 | |
| No | 1,885 (68) | 24.0 ± 8.7 | Reference |  | reference |  | |
| Yes | 868 (32) | 23.7 ± 8.3 | -1.2 (-3.9, 1.7) |  | -0.1 (-2.6, 2.4) |  | |
|  |  |  |  |  |  |  | |
| Gout medications |  |  |  | 0.74 |  | 0.76 | |
| No gout | 2,691 (98) | 23.9 ± 8.6 | reference |  | reference |  | |
| Gout, no preventive treatment | 7 (0.3) | 21.7 ± 5.3 | -5.8 (-27.5, 22.4) |  | -2.1 (-22.6, 23.8) |  | |
| Gout, preventive treatment | 55 (2.0) | 24.3 ± 7.6 | 3.1 (-6.2, 13.3) |  | 3.1 (-5.1, 11.9) |  | |

1Values are mean ± SD

2Estimate is the percent difference in baseline serum 25(OH) vitamin D level compared with reference group. Adjusted model is adjusted for the variables in final model shown in Table 2.

3H2 blocker and proton pump inhibitor use is ≥ once per week – the others have no frequency restrictions.

Supplemental Table 3. Factors associated with response to 1000 IU/day cholecalciferol among optimally adherent1 participants2

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Randomized to Cholecalciferol  (*n* = 875) | Randomized to Placebo  (*n* = 892) | Univariate | | Multivariable Model  R2 = 0.53  *(n* = 1,766) | |
|  | *n* (%) | *n* (%) | Estimate3  % (95% CI) | *P* | Estimate3  % (95% CI) | *P* |
|  |  |  |  |  |  |  |
| Baseline serum vitamin D, ng/mL4 |  |  |  | <0.0001 |  | <0.0001 |
| 25th percentile=18.2 |  |  | 47.0 (42.6, 51.6) |  | 57.6 (49.7, 65.9) |  |
| 50th percentile=23.2 |  |  | 38.1 (34.8, 41.4) |  | 50.3 (42.8, 58.3) |  |
| 75th percentile=30.0 |  |  | 29.3 (25.5, 33.3) |  | 43.1 (35.1, 51.7) |  |
|  |  |  |  |  |  |  |
| Demographic factors |  |  |  |  |  |  |
| Sex |  |  |  | <0.0001 |  | <0.0001 |
| Male | 589 (67) | 580 (65) | 32.6 (28.7, 36.6) |  | 42.4 (34.9, 50.2) |  |
| Female | 286 (33) | 312 (35) | 48.1 (42.1, 54.4) |  | 57.9 (48.7, 67.7) |  |
|  |  |  |  |  |  |  |
| Race |  |  |  | <0.0001 |  | 0.02 |
| White | 751 (86) | 761 (85) | 34.5 (31.1, 38.0) |  | 41.3 (37.1, 45.7) |  |
| Black | 63 (7.2) | 57 (6.4) | 73.1 (57.9, 89.8) |  | 60.2 (46.4, 75.3) |  |
| Asian/Pacific Islander | 22 (2.5) | 24 (2.7) | 57.2 (35.5, 82.3) |  | 58.8 (37.8, 83.0) |  |
| Other/unknown/refused | 39 (4.5) | 50 (5.6) | 40.3 (26.0, 56.2) |  | 40.5 (26.8, 55.6) |  |
|  |  |  |  |  |  |  |
| Sun-related factors |  |  |  |  |  |  |
| Season of baseline blood draw |  |  |  | <0.0001 |  | 0.004 |
| December-February | 193 (22) | 184 (21) | 56.9 (49.1, 65.1) |  | 55.6 (44.0, 68.1) |  |
| March-May | 210 (24) | 232 (26) | 27.3 (21.4, 33.4) |  | 36.5 (26.9, 46.8) |  |
| June-August | 246 (28) | 238 (27) | 29.2 (23.5, 35.1) |  | 52.0 (41.7, 63.1) |  |
| September-November | 226 (26) | 238 (27) | 42.8 (36.4, 49.5) |  | 56.5 (45.7, 68.2) |  |
|  |  |  |  |  |  |  |
| Season of Year 1 blood draw |  |  |  | <0.0001 |  | 0.0004 |
| December-February | 209 (24) | 215 (24) | 47.2 (40.4, 54.4) |  | 55.1 (44.2, 66.9) |  |
| March-May | 217 (25) | 213 (24) | 54.7 (47.6, 62.2) |  | 64.3 (53.0, 76.4) |  |
| June-August | 223 (25) | 219 (25) | 26.3 (20.6, 32.3) |  | 45.4 (34.9, 56.7) |  |
| September-November | 226 (26) | 245 (27) | 25.4 (19.9, 31.2) |  | 36.4 (26.8, 46.6) |  |
|  |  |  |  |  |  |  |
| Wears pants / sleeves in 3 month period when outside the most |  |  |  | 0.0001 |  | 0.01 |
| Never/rarely (0-10%) | 446 (51) | 461 (52) | 31.8 (27.4, 36.3) |  | 43.2 (35.4, 51.4) |  |
| Sometimes (11-50%) | 145 (17) | 160 (18) | 34.9 (27.3, 42.9) |  | 43.9 (34.3, 54.3) |  |
| Usually (51-85%) | 86 (9.8) | 81 (9.1) | 47.9 (36.7, 60.0) |  | 57.1 (44.2, 71.2) |  |
| Almost Always (86-100%) | 198 (23) | 189 (21) | 50.3 (42.8, 58.3) |  | 56.1 (46.1, 66.7) |  |
|  |  |  |  |  |  |  |
| Latitude of study center |  |  |  | 0.002 |  |  |
| Northern 43-450 | 236 (27) | 247 (28) | 45.9 (39.8, 52.3) |  |  |  |
| 35-420 | 352 (40) | 357 (40) | 35.6 (30.5, 40.8) |  |  |  |
| Southern <350 | 287 (33) | 288 (32) | 31.4 (25.4, 37.6) |  |  |  |
|  |  |  |  |  |  |  |
| Health-related factors |  |  |  |  |  |  |
| Menopausal status at baseline |  |  |  | 0.01 |  |  |
| Pre | 53 (19) | 67 (22) | 31.1 (18.9, 44.5) |  |  |  |
| Post | 231 (81) | 239 (78) | 52.3 (45.1, 59.9) |  |  |  |
|  |  |  |  |  |  |  |
| Behavioral factors |  |  |  |  |  |  |
| Activity level5 |  |  |  | 0.0003 |  |  |
| Low | 213 (25) | 207 (24) | 46.4 (39.3, 53.9) |  |  |  |
| Moderate | 280 (32) | 273 (31) | 42.1 (36.1, 48.4) |  |  |  |
| High | 373 (43) | 401 (46) | 30.4 (25.7, 35.3) |  |  |  |
|  |  |  |  |  |  |  |
| Alcohol intake, grams/d |  |  |  | 0.01 |  |  |
| ≤1 | 247 (31) | 266 (32) | 46.4 (40.0, 53.0) |  |  |  |
| 1.1 - 13.5 | 304 (38) | 332 (40) | 33.5 (28.3, 38.9) |  |  |  |
| 13.6-30 | 138 (17) | 129 (15) | 35.5 (27.4, 44.1) |  |  |  |
| >30 | 114 (14) | 112 (13) | 33.1 (24.5, 42.3) |  |  |  |
|  |  |  |  |  |  |  |
| Nutritional factors6 | | |  |  |  |  |
| Dietary vitamin D during Year 17 |  |  |  | 0.04 |  |  |
| Quartile 1 | 231 (26) | 218 (24) | 42.1 (35.5, 49.1) |  |  |  |
| Quartile 2 | 211 (24) | 228 (26) | 42.1 (35.3, 49.1) |  |  |  |
| Quartile 3 | 221 (25) | 217 (24) | 36.8 (30.4, 43.6) |  |  |  |
| Quartile 4 | 212 (24) | 229 (26) | 30.4 (24.3, 36.9) |  |  |  |
|  |  |  |  |  |  |  |
| Dietary calcium during Year 18 |  |  |  | 0.01 |  |  |
| Quartile 1 | 233 (27) | 228 (26) | 45.7 (39.0, 52.7) |  |  |  |
| Quartile 2 | 229 (26) | 208 (23) | 37.6 (31.1, 44.4) |  |  |  |
| Quartile 3 | 198 (23) | 218 (24) | 38.9 (32.2, 46.0) |  |  |  |
| Quartile 4 | 215 (25) | 238 (27) | 29.4 (23.4, 35.7) |  |  |  |

1Optimal adherence is the self-reported taking ≥80% of study pills, no personal vitamin D supplementation, and no gaps in pill-taking of ≥seven days.

2All variables are shown which had a univariate association with 25(OH)D response after testing all those in Supplemental Table 1. When numbers do not sum to column totals, this is due to missing data.

3Estimates are the percent change in serum 25(OH) vitamin D level from baseline to Year 1 relative to controls, adjusted for study center, colonoscopy surveillance follow-up interval (3 or 5 year), sex and randomization group (2- or 4-group).

4Percentiles of baseline 25(OH)D are derived from all participants with measured Year 1 25(OH)D. To assist interpretation: The equivalent Year 1 serum 25(OH) vitamin D concentration for participants with median baseline level (23.2 ng/mL) and an increase of 20% would be 27.8 ng/mL; 25% (29.0 ng/mL), 30% (30.2 ng/mL), 35% (31.3 ng/mL), 40% (32.5 ng/mL)

5High activity: vigorous activity on ≥3 days/week achieving ≥1500 Metabolic Equivalent of Task (MET)-minutes/week OR 7 days of any combination of activities achieving ≥3000 MET-minutes/week. Moderate activity: ≥3 days/week of vigorous activity of ≥20 minutes/day OR ≥5 days of moderate activity and/or walking of ≥30 minutes/day OR ≥5 days of any activity achieving ≥600 MET-minutes/week. Low: less than moderate activity level.

6 Sex-specific quartiles are calculated for the whole study population.

7 Cut points for dietary vitamin D quartiles, IU/day: men (26.6, 59.65, 114.15); women (18.05, 42.6, 101.8)

8 Cut points for dietary calcium quartiles mg/day: men (251.63, 384.35, 589.65); women (206.80, 317.50, 497.90)

Supplemental Table 4. Factors associated with baseline serum 25-hydroxyvitamin D among non Hispanic whites1

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  |  | Univariate model |  | Multivariable model  R2 = 0.28  *(n* = 2,013) | | Multivariable model  including SNPs2  R2 = 0.29  *(n* = 1,603) | |
|  | | *n* | Baseline 25(OH)D, ng/mL3 | Estimate4  % (95% CI) | *P* | Estimate4  % (95% CI) | *P* | Estimate4  % (95% CI) | *P* |
| Demographic factors | |  |  |  |  |  |  |  |  |
| Sex | |  |  |  | 0.047 |  |  |  |  |
| Male | | 1,386 | 25.1 ± 8.5 | Reference |  |  |  |  |  |
| Female | | 805 | 24.5 ± 8.8 | -3.0 (-5.8, -0.0) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| Year of blood draw | |  |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| 2004 | | 202 | 26.9 ± 8.8 | Reference |  | Reference |  | Reference |  |
| 2005 | | 590 | 26.8 ± 9.0 | -0.9 (-6.1, 4.6) |  | 4.7 (-0.5, 10.2) |  | 5.6 (0.2, 11.4) |  |
| 2006 | | 686 | 23.6 ± 7.8 | -12.3 (-16.8, -7.5) |  | -6.5 (-11.1, -1.7) |  | -7.9 (-12.7, -2.9) |  |
| 2007 | | 533 | 23.7 ± 8.8 | -12.8 (-17.4, -7.9) |  | -7.1 (-11.8, -2.1) |  | -8.0 (-12.9, -2.8) |  |
| 2008 | | 180 | 24.5 ± 8.5 | -9.4 (-15.4, -3.1) |  | -0.9 (-7.1, 5.8) |  | -2.0 (-8.5, 5.0) |  |
|  | |  |  |  |  |  |  |  |  |
| Sun-related factors | |  |  |  |  |  |  |  |  |
| Season of blood draw | |  |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| December-February | | 492 | 23.3 ± 7.9 | Reference |  | Reference |  | Reference |  |
| March-May | | 567 | 22.4 ± 8.1 | -4.4 (-8.2, -0.5) |  | -4.4 (-7.9, -0.8) |  | -2.2 (-6.0, 1.7) |  |
| June-August | | 590 | 27.1 ± 8.6 | 17.0 (12.5, 21.8) |  | 16.7 (12.5, 21.1) |  | 16.5 (12.1, 21.1) |  |
| September-November | | 542 | 26.6 ± 8.9 | 14.4 (9.9, 19.2) |  | 12.2 (8.0, 16.6) |  | 9.6 (5.3, 14.0) |  |
|  | |  |  |  |  |  |  |  |  |
| Latitude of study center | |  |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| Northern 43-450 | | 724 | 23.7 ± 8.6 | Reference |  | Reference |  | Reference |  |
| 35-420 | | 862 | 25.7 ± 8.8 | 9.1 (5.5, 12.8) |  | 7.5 (4.3, 10.9) |  | 7.5 (4.1, 11.0) |  |
| Southern <350 | | 605 | 25.0 ± 8.4 | 6.3 (2.5, 10.3) |  | 9.5 (5.8, 13.3) |  | 8.6 (4.7, 12.7) |  |
|  | |  |  |  |  |  |  |  |  |
| Artificial tanning | |  |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| No | | 2,107 | 24.6 ± 8.4 | Reference |  | Reference |  | Reference |  |
| Yes | | 81 | 32.8 ± 10.6 | 33.9 (24.2, 44.3) |  | 27.1 (18.8, 35.9) |  | 25.7 (17.1, 34.9) |  |
|  | |  |  |  |  |  |  |  |  |
| Sunscreen use | |  |  |  | <0.0001 |  |  |  |  |
| Never/rarely (0-10%) | | 1,074 | 24.0 ± 8.6 | Reference |  |  |  |  |  |
| Sometimes (11-85%) | | 933 | 25.5 ± 8.5 | 7.1 (4.0, 10.3) |  |  |  |  |  |
| Almost always (86-100%) | | 181 | 26.6 ± 9.0 | 11.4 (5.6, 17.5) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Wears pants / sleeves in 3 month period when outside most |  | |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| Never/rarely (0-10%) | 1,167 | | 26.0 ± 8.8 | Reference |  | Reference |  | Reference |  |
| Sometimes (11-50%) | 394 | | 25.0 ± 8.4 | -3.9 (-7.5, -0.1) |  | -3.6 (-6.9, -0.1) |  | -4.0 (-7.5, -0.3) |  |
| Usually (51-85%) | 195 | | 23.4 ± 8.2 | -10.1 (-14.6, -5.4) |  | -6.5 (-10.8, -2.1) |  | -8.4 (-12.9, -3.8) |  |
| Almost always (86-100%) | | 431 | 22.3 ± 8.0 | -14.9 (-18.0, -11.7) |  | -12.3 (15.2, -9.2) |  | -10.5 (-13.6, -7.3) |  |
|  | |  |  |  |  |  |  |  |  |
| Vacation days in warm climate | |  |  |  | <0.0001 |  |  |  |  |
| None | | 936 | 23.8 ± 8.4 | Reference |  |  |  |  |  |
| 1 - 7 | | 517 | 25.5 ± 8.9 | 7.1 (3.3, 11.1) |  |  |  |  |  |
| 8 - 14 | | 363 | 25.9 ± 8.9 | 9.1 (4.7, 13.7) |  |  |  |  |  |
| 15 - 120 | | 374 | 25.7 ± 8.4 | 8.9 (4.5, 13.4) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| Health-related factors | | |  |  |  |  |  |  |  |
| Diabetes |  | |  |  | 0.002 |  |  |  |  |
| No history | 2,025 | | 25.1 ± 8.7 | Reference |  |  |  |  |  |
| Diet controlled | 34 | | 24.1 ± 8.1 | -3.4 (-13.9, 8.5) |  |  |  |  |  |
| Non-insulin dependent | 107 | | 22.6 ± 7.4 | -9.6 (-15.4, -3.3) |  |  |  |  |  |
| Insulin dependent | 25 | | 20.7 ± 6.2 | -16.3 (-26.8, -4.2) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Ever had hypertension |  | |  |  | 0.003 |  |  |  |  |
| No | 1,416 | | 25.3 ± 8.8 | Reference |  |  |  |  |  |
| Yes | 774 | | 24.1 ± 8.3 | -4.4 (-7.2, -1.5) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Ever had high cholesterol |  | |  |  | 0.004 |  |  |  |  |
| No | 1,157 | | 25.4 ± 8.9 | Reference |  |  |  |  |  |
| Yes | 1,028 | | 24.3 ± 8.3 | -4.2 (-6.9, -1.4) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Taking oral corticosteroid |  | |  |  | 0.01 |  |  |  |  |
| No | 2,164 | | 24.9 ± 8.7 | Reference |  |  |  |  |  |
| Yes | 27 | | 20.7 ± 6.1 | -15.8 (-26.0, -4.1) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Taking a statin |  | |  |  | 0.04 |  |  |  |  |
| No | 1,487 | | 25.2 ± 8.8 | Reference |  |  |  |  |  |
| Yes | 704 | | 24.3 ± 8.3 | -3.2 (-6.1, -0.2) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Taking warfarin |  | |  |  | 0.01 |  |  |  |  |
| No | 2,165 | | 24.9 ± 8.7 | Reference |  |  |  |  |  |
| Yes | 26 | | 20.7 ± 6.3 | -16.1 (-26.5, -4.2) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Taking cholesterol-lowering drug |  | |  |  | 0.049 |  |  |  |  |
| No | 1,432 | | 25.2 ± 8.8 | Reference |  |  |  |  |  |
| Yes | 759 | | 24.4 ± 8.3 | -3.0 (-5.9, -0.0) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Taking any diuretic |  | |  |  | <0.0001 |  |  |  |  |
| No | 1,828 | | 25.2 ± 8.7 | Reference |  |  |  |  |  |
| Yes | 363 | | 23.2 ± 8.0 | -8.0 (-11.5, -4.4) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Taking proton pump inhibitor |  | |  |  | 0.001 |  |  |  |  |
| No | 1,897 | | 25.1 ± 8.7 | Reference |  |  |  |  |  |
| Yes | 294 | | 23.4 ± 8.1 | -7.1 (-10.9, -3.1) |  |  |  |  |  |
|  |  | |  |  |  |  |  |  |  |
| Behavioral factors |  | |  |  |  |  |  |  |  |
| Body mass index |  | |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| <25 | 489 | | 27.0 ± 9.0 | Reference |  | Reference |  | Reference |  |
| 25 - 29 | 891 | | 25.3 ± 8.3 | -6.2 (-9.6, -2.7) |  | -6.5 (-9.6, -3.3) |  | -5.7 (-9.0, -2.4) |  |
| 30 - 34 | 549 | | 24.3 ± 8.6 | -10.3 (-13.9, -6.6) |  | -10.6 (-13.9, -7.2) |  | -8.2 (-11.8, -4.5) |  |
| ≥35 | 259 | | 20.8 ± 7.4 | -23.2 (-27.0, -19.3) |  | -21.8 (-25.4, -18.0) |  | -17.6 (-21.6, -13.4) |  |
|  |  | |  |  |  |  |  |  |  |
| Smoking status |  | |  |  | 0.004 |  | 0.0002 |  | 0.10 |
| Never | 1,134 | | 24.7 ± 8.4 | Reference |  | Reference |  | Reference |  |
| Former | 842 | | 25.5 ± 8.8 | 2.9 (-0.2, 6.1) |  | 2.5 (-0.3, 5.4) |  | 2.4 (-0.5, 5.5) |  |
| Current | 215 | | 23.7 ± 9.2 | -5.5 (-10.1, -0.7) |  | -7.1 (-11.2, -2.7) |  | -2.4 (-7.1, 2.6) |  |
|  |  | |  |  |  |  |  |  |  |
| Alcohol intake, grams/d |  | |  |  | <0.0001 |  | 0.001 |  | 0.01 |
| ≤1 | 624 | | 23.6 ± 8.0 | Reference |  | Reference |  | Reference |  |
| 1.1 - 13.5 | 758 | | 25.1 ± 8.7 | 6.3 (2.5, 10.2) |  | 2.5 (-0.7, 5.8) |  | 1.8 (-1.5, 5.3) |  |
| 13.6-30 | 371 | | 25.8 ± 8.7 | 9.5 (4.8, 14.4) |  | 4.5 (0.5, 8.6) |  | 4.9 (0.7, 9.3) |  |
| >30 | 287 | | 26.5 ± 9.6 | 12.1 (6.8, 17.5) |  | 8.8 (4.3, 13.5) |  | 7.6 (2.9, 12.5) |  |
|  |  | |  |  |  |  |  |  |  |
| Activity level5 |  | |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| Low | 512 | | 23.4 ± 8.2 | Reference |  | Reference |  | Reference |  |
| Moderate | 698 | | 24.1 ± 8.2 | 3.3 (-0.6, 7.4) |  | 1.0 (-2.5, 4.6) |  | 2.1 (-1.6, 5.9) |  |
| High | 958 | | 26.1 ± 8.9 | 11.7 (7.8, 15.9) |  | 7.3 (3.7, 10.9) |  | 7.8 (4.1, 11.6) |  |
|  |  | |  |  |  |  |  |  |  |
| Nutritional factors | | | |  |  |  |  |  |  |
| Vitamin D intake via supplements, IU/d | | |  |  | <0.0001 |  |  |  |  |
| None | | 977 | 23.3 ± 8.4 | Reference |  |  |  |  |  |
| 1-399 | | 48 | 27.2 ± 7.9 | 19.2 (8.1, 31.4) |  |  |  |  |  |
| ≥400 | | 1,064 | 26.1 ± 8.6 | 13.1 (9.8, 16.4) |  |  |  |  |  |
| Unknown amount | | 102 | 26.8 ± 9.7 | 15.5 (7.8, 23.7) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| Calcium intake via supplements, mg/d | | | |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| None | | 953 | 23.2 ± 8.4 | Reference |  | Reference |  | Reference |  |
| 1-200 | | 639 | 25.6 ± 8.5 | 11.3 (7.6, 15.1) |  | 7.5 (4.2, 10.9) |  | 5.8 (2.5, 9.3) |  |
| >200 | | 456 | 27.1 ± 8.7 | 18.0 (13.6, 22.5) |  | 15.0 (11.1, 19.1) |  | 12.9 (8.9, 17.0) |  |
| Unknown amount | | 143 | 25.6 ± 8.9 | 10.9 (4.5, 17.6) |  | 9.9 (4.2, 16.0) |  | 6.6 (0.9, 12.6) |  |
|  | |  |  |  |  |  |  |  |  |
| Dairy servings6 | |  |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| Quartile7 1 | | 440 | 23.6 ± 8.4 | Reference |  | Reference |  | Reference |  |
| Quartile 2 | | 504 | 24.3 ± 8.8 | 2.7 (-1.7, 7.2) |  | 1.9 (-1.9, 5.8) |  | 2.8 (-1.3, 7.0) |  |
| Quartile 3 | | 529 | 24.7 ± 8.4 | 4.9 (0.5, 9.5) |  | 5.2 (1.3, 9.2) |  | 5.2 (1.2, 9.5) |  |
| Quartile 4 | | 568 | 26.8 ± 8.7 | 15.0 (10.3, 20.0) |  | 14.2 (10.0, 18.6) |  | 13.1 (8.7, 17.6) |  |
|  | |  |  |  |  |  |  |  |  |
| Dietary vitamin D intake8 | |  |  |  | <0.0001 |  |  |  |  |
| Quartile7 1 | | 501 | 24.2 ± 9.3 | Reference |  |  |  |  |  |
| Quartile 2 | | 501 | 24.5 ± 8.5 | 2.2 (-2.0, 6.6) |  |  |  |  |  |
| Quartile 3 | | 505 | 24.6 ± 8.3 | 2.7 (-1.6, 7.1) |  |  |  |  |  |
| Quartile 4 | | 534 | 26.4 ± 8.5 | 11.2 (6.7, 15.9) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| Dietary calcium intake9 | |  |  |  | <0.0001 |  |  |  |  |
| Quartile7 1 | | 464 | 23.8 ± 8.5 | Reference |  |  |  |  |  |
| Quartile 2 | | 501 | 24.7 ± 8.9 | 4.0 (-0.4, 8.6) |  |  |  |  |  |
| Quartile 3 | | 532 | 24.6 ± 8.4 | 4.0 (-0.3, 8.5) |  |  |  |  |  |
| Quartile 4 | | 544 | 26.5 ± 8.7 | 12.7 (8.1, 17.6) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| Dietary magnesium intake10 | |  |  |  | 0.01 |  |  |  |  |
| Quartile7 1 | | 504 | 24.3 ± 8.9 | Reference |  |  |  |  |  |
| Quartile 2 | | 518 | 24.8 ± 8.7 | 2.4 (-1.8, 6.8) |  |  |  |  |  |
| Quartile 3 | | 515 | 24.7 ± 8.1 | 2.8 (-1.5, 7.2) |  |  |  |  |  |
| Quartile 4 | | 504 | 25.9 ± 9.0 | 7.4 (2.9, 12.0) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| Multivitamin use | |  |  |  | <0.0001 |  |  |  |  |
| No | | 983 | 23.4 ± 8.4 | Reference |  |  |  |  |  |
| Yes | | 1,205 | 26.0 ± 8.6 | 12.1 (8.9, 15.3) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| SNPs | |  |  |  |  |  |  |  |  |
| *GC*: | |  |  |  |  |  |  |  |  |
| rs228267911 | |  |  |  | <0.0001 |  |  |  |  |
| TT (ref) | | 964 | 26.5 ± 8.8 |  |  |  |  |  |  |
| TG | | 661 | 24.6 ± 8.1 | -7.0 (-9.9, -4.1) |  |  |  |  |  |
| GG | | 137 | 21.4 ± 6.3 | -18.5 (-23.0, -13.8) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| rs375596711 | |  |  |  | <0.0001 |  |  |  |  |
| CC (ref) | | 943 | 26.5 ± 8.7 |  |  |  |  |  |  |
| CT | | 660 | 24.7 ± 8.2 | -6.8 (-9.7, -3.8) |  |  |  |  |  |
| TT | | 135 | 21.3 ± 6.4 | -18.7 (-23.3, -14.0) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| rs4588 | |  |  |  | <0.0001 |  |  |  | <0.0001 |
| CC (ref) | | 940 | 26.5 ± 8.7 |  |  |  |  | Reference |  |
| AC | | 660 | 24.5 ± 8.1 | -7.4 (-10.3, -4.4) |  |  |  | -7.9 (-10.5, -5.3) |  |
| AA | | 137 | 21.3 ± 6.3 | -18.8 (-23.2, -14.0) |  |  |  | -18.9 (-23.1, -14.6) |  |
|  | |  |  |  |  |  |  |  |  |
| rs7041 | |  |  |  | <0.0001 |  |  |  |  |
| CC (ref) | | 588 | 26.7 ± 8.9 |  |  |  |  |  |  |
| AC | | 833 | 25.4 ± 8.4 | -4.8 (-7.9, -1.5) |  |  |  |  |  |
| AA | | 327 | 23.1 ± 7.6 | -13.3 (-16.9, -9.5) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| rs1155563 | |  |  |  | <0.0001 |  |  |  |  |
| TT (ref) | | 947 | 26.5 ± 8.7 |  |  |  |  |  |  |
| TC | | 657 | 24.4 ± 8.2 | -8.1 (-10.9, -5.1) |  |  |  |  |  |
| CC | | 138 | 22.0 ± 7.0 | -16.7 (-21.3, -11.9) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| rs12512631 | |  |  |  | 0.0002 |  |  |  |  |
| TT (ref) | | 708 | 24.4 ± 8.2 |  |  |  |  |  |  |
| TC | | 810 | 25.9 ± 8.4 | 6.4 (3.0, 9.8) |  |  |  |  |  |
| CC | | 241 | 26.3 ± 8.9 | 7.4 (2.5, 12.5) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| *CYP2R1*: | |  |  |  |  |  |  |  |  |
| rs12794714 | |  |  |  | <0.0001 |  |  |  |  |
| GG (ref) | | 556 | 26.6 ± 9.0 |  |  |  |  |  |  |
| GA | | 874 | 25.2 ± 8.3 | -4.7 (-7.9, -1.4) |  |  |  |  |  |
| AA | | 338 | 23.8 ± 7.4 | -9.5 (-13.3, -5.5) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| rs10741657 | |  |  |  | <0.0001 |  |  |  | 0.0002 |
| GG (ref) | | 644 | 24.3 ± 7.6 |  |  |  |  | Reference |  |
| GA | | 832 | 25.5 ± 8.6 | 4.1 (0.7, 7.6) |  |  |  | 3.5 (0.5, 6.6) |  |
| AA | | 288 | 27.3 ± 9.4 | 11.0 (6.2, 16.1) |  |  |  | 8.7 (4.5, 13.1) |  |
|  | |  |  |  |  |  |  |  |  |
| rs206079312 | |  |  |  | <0.0001 |  |  |  |  |
| CC (ref) | | 645 | 24.3 ± 7.6 |  |  |  |  |  |  |
| CT | | 833 | 25.5 ± 8.6 | 3.9 (0.6, 7.4) |  |  |  |  |  |
| TT | | 278 | 27.4 ± 9.6 | 11.4 (6.5, 16.6) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| rs1562902 | |  |  |  | 0.003 |  |  |  |  |
| AA (ref) | | 550 | 24.6 ± 7.9 |  |  |  |  |  |  |
| AG | | 853 | 25.3 ± 8.4 | 2.0 (-1.4, 5.6) |  |  |  |  |  |
| GG | | 365 | 26.8 ± 9.4 | 7.5 (3.1, 12.2) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |
| rs10766197 | |  |  |  | 0.001 |  |  |  |  |
| GG (ref) | | 509 | 26.5 ± 9.0 |  |  |  |  |  |  |
| GA | | 870 | 25.1 ± 8.3 | -4.9 (-8.2, -1.6) |  |  |  |  |  |
| AA | | 376 | 24.4 ± 8.1 | -7.3 (-11.2, -3.3) |  |  |  |  |  |
|  | |  |  |  |  |  |  |  |  |

1All variables are shown which had a univariate association with 25(OH) vitamin D after testing all those in Supplemental Table 1. When numbers do not sum to 2,191, this is due to missing data.

2Values are mean ± SD

3Estimates are the percent difference in baseline serum 25(OH) vitamin D level compared with reference group.

4The number in the model is smaller than expected because genotyping was not done on non-randomized participants.

5High activity: vigorous activity on ≥3 days/week achieving ≥1500 Metabolic Equivalent of Task (MET)-minutes/week OR 7 days of any combination of activities achieving ≥3000 MET-minutes/week. Moderate activity: ≥3 days/week of vigorous activity of ≥20 minutes/day OR ≥5 days of moderate activity and/or walking of ≥30 minutes/day OR ≥5 days of any activity achieving ≥600 MET-minutes/week. Low: less than moderate activity level.

6Cut points for dairy serving quartiles: men (0.6, 1.0, 1.7); women (0.5, 1.0, 1.5)

7 Sex-specific quartiles derived from all enrolled participants with baseline serum 25(OH) vitamin D were used in nutrition analyses

8 Cut points for dietary vitamin D quartiles, IU/day: men (67.31, 109.12, 176.10); women (57.37, 99.80, 157.35)

9 Cut points for dietary calcium quartiles, mg/day: men (444.6, 612.1, 840.8); women (397.5, 559.4, 784.5)

10 Cut points for dietary magnesium quartiles, mg/day: men (188.0, 242.6, 310.7); women (159.8, 206.0, 266.9)

11 Linkage Disequilibrium r2=0.97 with rs4588; not included in group model

12 Linkage Disequilibrium r2=0.99 with rs10741657; not included in group model

Supplemental Table 5. Factors associated with serum response to 1000 IU/day cholecalciferol among non Hispanic whites1

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Randomized to Cholecalciferol  (*n* = 905) | Randomized to Placebo (*n* = 904) | Univariate | | Multivariable Model  R2 = 0.48  *(n* = 1,806) | | Multivariable Model  with SNP  R2 = 0.48  *(n* = 1,721) | |
|  | *n* (%) | *n* (%) | Estimate2  % (95% CI) | *P* | Estimate2  % (95% CI) | *P* | Estimate2  % (95% CI) | *P* |
|  |  |  |  |  |  |  |  |  |
| Baseline serum 25(OH)D, ng/mL3 |  |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| 25th percentile=18.2 |  |  | 39.5 (35.1, 44.1) |  | 39.6 (26.3, 54.2) |  | 42.8 (29.0, 58.1) |  |
| 50th percentile=23.2 |  |  | 33.2 (30.0, 36.5) |  | 33.8 (21.4, 47.6) |  | 36.5 (23.5, 50.8) |  |
| 75th percentile=30.0 |  |  | 26.9 (23.3, 30.6) |  | 28.1 (16.0, 41.5) |  | 30.1 (17.6, 44.0) |  |
|  |  |  |  |  |  |  |  |  |
| Optimal adherence4 |  |  |  | 0.01 |  | 0.01 |  | 0.01 |
| No | 166 (18) | 158 (18) | 23.1 (16.3, 30.3) |  | 26.9 (14.9, 40.2) |  | 29.4 (16.9, 43.2) |  |
| Yes | 739 (82) | 745 (83) | 34.4 (30.9, 38.0) |  | 39.2 (25.1, 55.0) |  | 41.9 (27.1, 58.3) |  |
|  |  |  |  |  |  |  |  |  |
| Demographic factors |  |  |  |  |  |  |  |  |
| Sex |  |  |  | 0.0002 |  | <0.0001 |  | <0.0001 |
| Male | 581 (64) | 583 (64) | 27.7 (24.0, 31.6) |  | 25.8 (13.8, 39.0) |  | 27.9 (15.4, 41.6) |  |
| Female | 324 (36) | 321 (36) | 40.7 (35.2, 46.5) |  | 40.5 (27.0, 55.4) |  | 43.5 (29.5, 59.1) |  |
|  |  |  |  |  |  |  |  |  |
| Sun-related factors |  |  |  |  |  |  |  |  |
| Season of baseline blood draw |  |  |  | <0.0001 |  | 0.01 |  | 0.01 |
| December-February | 206 (23) | 197 (22) | 45.2 (38.1, 52.6) |  | 35.1 (20.6, 51.3) |  | 38.5 (23.4, 55.4) |  |
| March-May | 223 (25) | 237 (26) | 23.2 (17.6, 29.1) |  | 22.0 (9.6, 35.8) |  | 24.3 (11.3, 38.7) |  |
| June-August | 243 (27) | 243 (27) | 26.6 (21.0, 32.4) |  | 37.4 (23.0, 53.6) |  | 40.6 (25.6, 57.5) |  |
| September-November | 233 (26) | 227 (25) | 37.9 (31.6, 44.5) |  | 37.9 (23.4, 54.0) |  | 39.2 (24.3, 55.9) |  |
|  |  |  |  |  |  |  |  |  |
| Season of Year 1 blood draw |  |  |  | <0.0001 |  | 0.001 |  | 0.001 |
| December-February | 217 (24) | 215 (24) | 41.9 (35.3, 48.8) |  | 39.8 (25.3, 56.0) |  | 44.4 (29.2, 61.5) |  |
| March-May | 222 (25) | 211 (23) | 43.8 (37.1, 50.8) |  | 43.4 (28.3, 60.2) |  | 43.8 (28.5, 61.0) |  |
| June-August | 237 (26) | 234 (26) | 23.5 (18.0, 29.3) |  | 29.0 (15.3, 44.3) |  | 32.0 (17.7, 48.0) |  |
| September-November | 229 (25) | 244 (27) | 22.9 (17.4, 28.7) |  | 20.8 (8.3, 34.7) |  | 22.8 (9.9, 37.3) |  |
|  |  |  |  |  |  |  |  |  |
| Wears pants sleeves in 3 month period when outside most |  |  |  | 0.0003 |  | 0.002 |  | 0.001 |
| Never/rarely (0-10%) | 481 (53) | 499 (55) | 27.1 (23.1, 31.4) |  | 25.2 (13.6, 38.0) |  | 26.7 (14.7, 39.9) |  |
| Sometimes (11-50%) | 145 (16) | 169 (19) | 31.3 (24.0, 39.2) |  | 28.7 (15.3, 43.5) |  | 31.7 (17.7, 47.2) |  |
| Usually (51-85%) | 84 (9) | 70 (8) | 42.5 (31.1, 54.7) |  | 40.2 (23.9, 58.6) |  | 43.8 (26.6, 63.2) |  |
| Almost Always (86-100%) | 194 (21) | 165 (18) | 44.3 (36.7, 52.4) |  | 38.3 (24.5, 53.5) |  | 40.4 (26.2, 56.2) |  |
|  |  |  |  |  |  |  |  |  |
| Behavioral factors |  |  |  |  |  |  |  |  |
| Activity level5 |  |  |  | 0.001 |  |  |  |  |
| Low | 221 (25) | 197 (22) | 37.8 (31.1, 44.9) |  |  |  |  |  |
| Moderate | 288 (32) | 288 (32) | 38.6 (32.8, 44.6) |  |  |  |  |  |
| High | 386 (43) | 410 (46) | 25.7 (21.2, 30.4) |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| Health-related factors |  |  |  |  |  |  |  |  |
| Taking anticonvulsants during Year 1 | | | | 0.02 |  |  |  |  |
| No | 822 (97) | 882 (98) | 31.7 (28.5, 34.9) |  |  |  |  |  |
| Yes | 23 (2.5) | 21 (2.3) | 58.7 (35.8, 85.3) |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| Nutritional factors | |  |  |  |  |  |  |  |
| Personal calcium supplementation during Year 1, mg/day | | | | 0.046 |  |  |  |  |
| None | 856 (95) | 866 (96) | 33.2 (30.0, 36.6) |  |  |  |  |  |
| 1-200 | 38 (4.2) | 22 (2.4) | 16.5 (1.5, 33.8) |  |  |  |  |  |
| >200 | 11 (1.2) | 15 (1.7) | 11.8 (-8.8, 37.1) |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| Personal vitamin D supplementation during Year 1, IU/day | | | | 0.001 |  | 0.01 |  | 0.01 |
| None | 861 (95) | 865 (96) | 33.0 (29.7, 36.3) |  | 42.9 (33.4, 53.1) |  | 44.0 (34.2, 54.4) |  |
| 1-399 | 28 (3.1) | 25 (2.8) | 33.8 (16.2, 54.1) |  | 51.4 (30.4, 75.7) |  | 55.9 (33.6, 82.0) |  |
| ≥400 | 16 (1.8) | 13 (1.4) | -7.6 (-23.7, 11.8) |  | 8.6 (-10.5, 31.7) |  | 10.8 (-9.0, 34.8) |  |
|  |  |  |  |  |  |  |  |  |
| Fish oil supplementation during Year 1 | | | | 0.046 |  | 0.046 |  | 0.03 |
| No | 864 (95) | 876 (97) | 31.6 (28.4, 34.8) |  | 25.0 (15.5, 35.1) |  | 26.9 (17.0, 37.5) |  |
| Yes | 41 (4.5) | 27 (3.0) | 50.2 (32.2, 70.6) |  | 41.4 (22.6, 63.1) |  | 44.7 (25.2, 67.1) |  |
|  |  |  |  |  |  |  |  |  |
| SNPs |  |  |  |  |  |  |  |  |
| *CYP2R1*: |  |  |  |  |  |  |  |  |
| rs10766197 |  |  |  | 0.02 |  |  |  | 0.001 |
| GG | 247 (29) | 256 (30) | 39.4 (33.2, 46.0) |  |  |  | 44.8 (30.2, 60.9) |  |
| AG | 426 (49) | 429 (50) | 28.3 (23.8, 32.9) |  |  |  | 31.5 (18.6, 45.6) |  |
| AA | 193 (22) | 173 (20) | 30.7 (23.9, 37.9) |  |  |  | 30.7 (17.2, 45.6) |  |

1All variables are shown which had a univariate association with 25(OH) vitamin D response after testing all those shown in Supplemental Table 1. When numbers do not sum to column totals, this is due to missing data. When number in the model is smaller than expected, this is because genotyping was not done on non-randomized participants.

2Estimates are the percent change in serum 25(OH) vitamin D level from baseline to Year 1 relative to controls, adjusted for study center, colonoscopy surveillance follow-up interval (3 or 5 year), sex and randomization group (2 or 4-group).

3Percentiles of baseline 25(OH)D are derived from all participants with measured Year 1 25(OH)D. To assist interpretation: The equivalent Year 1 serum 25(OH) vitamin D concentration for participants with median baseline level (23.2 ng/mL) and an increase of 20% would be 27.8 ng/mL; 25% (29.0 ng/mL), 30% (30.2 ng/mL), 35% (31.3 ng/mL), 40% (32.5 ng/mL)

4Optimal adherence is the self-reported taking ≥80% of study pills during Year 1, no personal vitamin D supplementation, and no gaps in pill-taking of seven days or more

5High activity: vigorous activity on ≥3 days/week achieving ≥1500 Metabolic Equivalent of Task (MET)-minutes/week OR 7 days of any combination of activities achieving ≥3000 MET-minutes/week. Moderate activity: ≥3 days/week of vigorous activity of ≥20 minutes/day OR ≥5 days of moderate activity and/or walking of ≥30 minutes/day OR ≥5 days of any activity achieving ≥600 MET-minutes/week. Low: less than moderate activity level.

Supplemental Table 6. Factors associated with serum response to 1000 IU/day cholecalciferol among optimally adherent non Hispanic whites1

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Randomized to Cholecalciferol  (*n* = 739) | Randomized to Placebo  (*n =* 745) | Univariate | | Multivariable model  R2 = 0.49  *(n* = 1,483) | | Multivariable model  with SNP  R2 =0.51  *(n* = 1,398) | |
|  | *n* (%) | *n* (%) | Estimate2  % (95% CI) | *P* | Estimate2  % (95% CI) | *P* | Estimate2  % (95% CI) | *P* |
|  |  |  |  |  |  |  |  |  |
| Baseline Serum3 25(OH)D, ng/mL |  |  |  | <0.0001 |  | <0.0001 |  | <0.0001 |
| 25th percentile=18.2 |  |  | 42.8 (38.0, 47.9) |  | 61.0 (50.4, 72.4) |  | 56.4 (44.7, 69.0) |  |
| 50th percentile=23.2 |  |  | 35.6 (32.1, 39.2) |  | 42.3 (37.8, 46.9) |  | 49.1 (38.3, 60.7) |  |
| 75th percentile=30.0 |  |  | 28.5 (24.6, 32.5) |  | 42.2 (32.9, 52.1) |  | 41.8 (31.2, 53.3) |  |
|  |  |  |  |  |  |  |  |  |
| Demographic factors |  |  |  |  |  |  |  |  |
| Sex |  |  |  | 0.0002 |  | <0.0001 |  | <0.0001 |
| Male | 497 (67) | 497 (67) | 29.8 (25.8, 34.0) |  | 33.6 (29.1, 38.3) |  | 40.1 (29.7, 51.2) |  |
| Female | 242 (33) | 248 (33) | 44.0 (37.6, 50.6) |  | 49.0 (42.1, 56.2) |  | 56.0 (43.6, 69.4) |  |
|  |  |  |  |  |  |  |  |  |
| Sun related factors |  |  |  |  |  |  |  |  |
| Season of baseline blood draw |  |  |  | <0.0001 |  | 0.02 |  | 0.01 |
| December-February | 161 (22) | 148 (20) | 51.7 (43.6, 60.3) |  | 44.2 (34.4, 54.7) |  | 51.9 (37.7, 67.6) |  |
| March-May | 182 (25) | 195 (26) | 25.0 (18.9, 31.4) |  | 28.8 (20.6, 37.4) |  | 34.5 (22.4, 47.9) |  |
| June-August | 200 (27) | 201 (27) | 26.9 (20.9, 33.2) |  | 45.6 (36.8, 55.1) |  | 53.0 (39.4, 67.9) |  |
| September-November | 196 (27) | 201 (27) | 39.2 (32.6, 46.1) |  | 46.6 (37.6, 56.1) |  | 52.6 (38.9, 67.8) |  |
|  |  |  |  |  |  |  |  |  |
| Season of Year 1 blood draw |  |  |  | <0.0001 |  | <0.0001 |  | 0.0003 |
| December-February | 175 (24) | 179 (24) | 44.8 (37.6, 52.4) |  | 48.4 (38.7, 58.7) |  | 57.1 (42.8, 73.0) |  |
| March-May | 180 (24) | 166 (22) | 50.4 (42.8, 58.4) |  | 55.8 (46.2, 66.1) |  | 60.5 (46.3, 76.1) |  |
| June-August | 192 (26) | 191 (26) | 23.7 (17.8, 30.0) |  | 35.9 (27.4, 45.0) |  | 43.0 (30.0, 57.4) |  |
| September-November | 192 (26) | 209 (28) | 23.1 (17.3, 29.1) |  | 26.2 (18.4, 34.5) |  | 32.2 (20.2, 45.5) |  |
|  |  |  |  |  |  |  |  |  |
| Wears pants sleeves in 3 month period when outside most |  |  |  | 0.0004 |  | 0.002 |  | 0.002 |
| Never/rarely (0-10%) | 389 (53) | 409 (55) | 29.2 (24.8, 33.9) |  | 33.2 (28.7, 37.8) |  | 39.3 (28.9, 50.5) |  |
| Sometimes (11-50%) | 120 (16) | 135 (18) | 31.2 (23.2, 39.7) |  | 34.7 (26.9, 43.0) |  | 40.3 (27.9, 53.8) |  |
| Usually (51-85%) | 68 (9.2) | 62 (8.3) | 45.2 (33.0, 58.4) |  | 48.6 (36.6, 61.7) |  | 56.5 (40.2, 74.7) |  |
| Almost Always (86-100%) | 162 (22) | 138 (19) | 47.8 (39.5, 56.5) |  | 48.7 (40.6, 57.3) |  | 56.0 (43.0, 70.2) |  |
|  |  |  |  |  |  |  |  |  |
| Behavioral factors |  |  |  |  |  |  |  |  |
| Activity level4 |  |  |  | 0.01 |  |  |  |  |
| Low | 186 (25) | 167 (23) | 41.7 (34.3, 49.5) |  |  |  |  |  |
| Moderate | 237 (32) | 226 (31) | 38.1 (31.8, 44.7) |  |  |  |  |  |
| High | 309 (42) | 344 (47) | 28.2 (23.3, 33.3) |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| Health indicators |  |  |  |  |  |  |  |  |
| Menopausal status (women) |  |  |  | 0.04 |  |  |  |  |
| Pre | 47 (20) | 62 (25) | 30.8 (18.4, 44.4) |  |  |  |  |  |
| Post | 194 (81) | 183 (75) | 47.5 (39.9, 55.4) |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| Calcium channel blocker use during Year 1 | | | | 0.04 |  |  |  |  |
| No | 694 (94) | 702 (94) | 35.3 (31.7, 38.9) |  |  |  |  |  |
| Yes | 45 (6.1) | 43 (5.8) | 20.5 (8.2, 34.2) |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| SNPs |  |  |  |  |  |  |  |  |
| *CYP2R1:* |  |  |  |  |  |  |  |  |
| rs10766197 |  |  |  | 0.04 |  |  |  | 0.01 |
| GG | 202 (29) | 211 (30) | 41.3 (34.5, 48.4) |  |  |  | 57.0 (44.3, 70.9) |  |
| AG | 352 (50) | 354 (50) | 30.8 (25.9, 35.8) |  |  |  | 44.0 (33.0, 55.8) |  |
| AA | 152 (22) | 147 (21) | 31.9 (24.5, 39.8) |  |  |  | 42.8 (30.7, 56.0) |  |
|  |  |  |  |  |  |  |  |  |
| *VDR:* |  |  |  |  |  |  |  |  |
| rs10783219 |  |  |  | 0.03 |  |  |  |  |
| AA | 294 (41) | 295 (41) | 40.0 (34.3, 45.9) |  |  |  |  |  |
| AT | 328 (46) | 340 (47) | 29.9 (24.9, 35.0) |  |  |  |  |  |
| TT | 89 (13) | 82 (11) | 31.6 (21.9, 42.1) |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| rs4516035 |  |  |  | 0.03 |  |  |  | 0.04 |
| TT | 242 (34) | 220 (31) | 28.5 (22.7, 34.7) |  |  |  | 40.8 (29.6, 52.9) |  |
| TC | 334 (47) | 369 (52) | 34.8 (29.8, 40.0) |  |  |  | 49.1 (37.8, 61.3) |  |
| CC | 139 (19) | 125 (18) | 42.5 (33.9, 51.6) |  |  |  | 53.8 (40.4, 68.5) |  |
|  |  |  |  |  |  |  |  |  |
| *CASR:* |  |  |  |  |  |  |  |  |
| rs172512215 |  |  |  | 0.01 |  |  |  | 0.02 |
| AA | 536 (75) | 544 (76) | 36.2 (32.1, 40.4) |  |  |  | 43.5 (38.2, 48.9) |  |
| AG | 164 (23) | 161 (22) | 25.8 (18.9, 32.9) |  |  |  | 33.6 (25.9, 41.8) |  |
| GG | 10 (1.4) | 12 (1.7) | 68.7 (36.1, 109.0) |  |  |  | 68.4 (36.9, 107.2) |  |
|  |  |  |  |  |  |  |  |  |
| rs1801725 |  |  |  | 0.01 |  |  |  | 0.02 |
| GG | 535 (75) | 546 (76) | 36.0 (32.0, 40.2) |  |  |  | 43.5 (38.2, 48.9) |  |
| GT | 164 (23) | 158 (22) | 26.0 (19.1, 33.2) |  |  |  | 33.6 (25.9, 41.8) |  |
| TT | 10 (1.4) | 12 (1.7) | 68.6 (36.0, 108.9) |  |  |  | 68.4 (36.9, 107.2) |  |
|  |  |  |  |  |  |  |  |  |

1All variables are shown which had a univariate association with 25(OH) vitamin D response after testing all those shown in Supplemental Table 1. When numbers do not sum to column totals, this is due to missing data. When number in the model is smaller than expected, this is because genotyping was not done on non-randomized participants.

2Estimates are the percent change in serum 25(OH) vitamin D level from baseline to Year 1 relative to controls, adjusted for study center, colonoscopy surveillance follow-up interval (3 or 5 year), sex and randomization group (2 or 4-group).

3Percentiles of baseline 25(OH)D are derived from all participants with measured Year 1 25(OH)D. To assist interpretation: The equivalent Year 1 serum 25(OH) vitamin D concentration for participants with median baseline level (23.2 ng/mL) and an increase of 20% would be 27.8 ng/mL; 25% (29.0 ng/mL), 30% (30.2 ng/mL), 35% (31.3 ng/mL), 40% (32.5 ng/mL)

4High activity: vigorous activity on ≥3 days/week achieving ≥1500 Metabolic Equivalent of Task (MET)-minutes/week OR 7 days of any combination of activities achieving ≥3000 MET-minutes/week. Moderate activity: ≥3 days/week of vigorous activity of ≥20 minutes/day OR ≥5 days of moderate activity and/or walking of ≥30 minutes/day OR ≥5 days of any activity achieving ≥600 MET-minutes/week. Low: less than moderate activity level.

5Linkage Disequilibrium r2=0.998 with rs1801725; not included in group model