**Supplementary Online Content**

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**Supplemental Table 1. Effects of Vitamin D3 vs Placebo on the Change in Each Outcome Associated with Baseline Participant Characteristics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **PTH (pg/mL)** | | **Total 1,25(OH)2D (pg/mL)** | | **Total 25(OH)D (ng/mL)** | | **Urine Calcium/creatinine (mg/g)** | |
| **Variable** | **Difference in change (95% CI)**a | **p-value** | **Difference in change (95% CI)**a | **P-value** | **Difference in change (95% CI)**a | **P-value** | **Difference in change (95% CI)**a | **P-value** |
| Age (per decade) | 2 (-2, 6) | 0.327 | 2 (-2, 5) | 0.399 | 1 (-1, 2) | 0.512 | -2 (-22, 19) | 0.862 |
| Sex |  |  |  |  |  |  |  |  |
| Female | Ref | 0.558 | Ref | 0.700 | Ref | 0.798 | Ref | 0.913 |
| Male | 2 (-5, 8) |  | 1 (-5, 7) |  | 0 (-3, 2) |  | -2 (-29, 26) |  |
| Race/ethnicity |  |  |  |  |  |  |  |  |
| White | Ref | 0.285 | Ref | 0.008 | Ref | 0.917 | Ref | 0.591 |
| Black | 1 (-7, 8) |  | 6 (-1, 13) |  | 1 (-3, 4) |  | -17 (-49, 15) |  |
| Hispanic | 7 (-3, 17) |  | 8 (0, 15) |  | -1 (-5, 4) |  | 0 (-42, 43) |  |
| Chinese | 5 (-2, 13) |  | -8 (-12, -4) |  | 0 (-4, 4) |  | -24 (-73, 25) |  |
| BMI (kg/m2) |  |  |  |  |  |  |  |  |
| < 25 | Ref | 0.132 | Ref | 0.030 | Ref | 0.615 | Ref | 0.697 |
| 25 - <30 | 1 (-6, 8) |  | 4 (-3, 12) |  | -2 (-6, 1) |  | -3 (-39, 32) |  |
| 30 - <35 | -9 (-18, 0) |  | 11 (4, 18) |  | -1 (-4, 3) |  | -23 (-63, 18) |  |
| > 35 | -8 (-20, 4) |  | 5 (-3, 13) |  | -2 (-6, 2) |  | -12 (-48, 24) |  |
| eGFR (per 10 mL/min/1.73m2) | -2 (-3, 0) | 0.071 | 0 (-2, 2) | 0.947 | 0 (-1, 1) | 0.789 | 2 (-7, 11) | 0.677 |
| Bioavailable 25(OH)D (per 1 ng/mL decrement) | -4 (-7, -1) | 0.009 | 1 (-2, 3) | 0.586 | 2 (1, 3) | 0.001 | 6 (-4, 16) | 0.210 |
| 25(OH)D (ng/mL) |  |  |  |  |  |  |  |  |
| < 20 | -14 (-24, -3) |  | 0 (-8, 7) |  | 6 (2, 9) |  | 11 (-23, 45) |  |
| 20 – <30 | 1 (-6, 7) |  | 5 (-2, 13) |  | 5 (2, 8) |  | 14 (-18, 46) |  |
| > 30 | Ref | 0.022 | Ref | 0.282 | Ref | <0.001 | Ref | 0.677 |
| Per 10 ng/mL decrement | -4 (-8, -1) | 0.011 | 1 (-2, 3) | 0.575 | 2 (1, 4) | 0.002 | 10 (-2, 22) | 0.101 |
| VDBP (per 1 SD increment) | 0 (-3, 3) | 0.936 | 1 (-3, 4) | 0.740 | 0 (-2, 1) | 0.407 | -1 (-14, 12) | 0.878 |
| VDMR tertiles |  |  |  |  |  |  |  |  |
| Tertile 1 | -10 (-18, -2) |  | 1 (-6, 8) |  | 5 (1, 8) |  | -1 (-38, 35) |  |
| Tertile 2 | -1 (-8, 5) |  | -1 (-8, 7) |  | 3 (0, 6) |  | 9 (-21, 39) |  |
| Tertile 3 | Ref | 0.062 | Ref | 0.900 | Ref | 0.033 | Ref | 0.802 |
| Per 1 SD decrement | -3 (-7, 0) | 0.055 | 1 (-2, 4) | 0.555 | 2 (0, 3) | 0.026 | -2 (-16, 11) | 0.724 |

PTH, parathyroid hormone; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; eGFR, estimated glomerular filtration rate; VDBP, vitamin D binding protein; VDMR, vitamin D metabolite ratio (24,25-dihydroxyvitamin D3 to 25(OH)D3).

aDifferences in change in each outcome after 16-weeks of treatment comparing vitamin D3 with placebo, adjusted for age, sex, race/ethnicity, BMI, eGFR and season at baseline exam, and accounts for missing data using multiple imputation.

**Supplemental Table 2. Associations of Baseline 25-Hydroxyvitamin D and Change in Parathyroid Hormone by Race/Ethnicity Among Participants Assigned to Vitamin D3**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Parathyroid Hormone (pg/mL)** | | | |
| **Baseline 25(OH)D (ng/mL)** | **N** | **Baseline, mean (SD)** | **After treatment, mean (SD)** | **Change from baseline, mean (95% CI)** | **Difference in change, mean (95% CI)**a |
| White |  |  |  |  |  |
| < 20 | 17 | 85 (42) | 63 (24) | -22 (-41, -3) | -22 (-30, -13) |
| > 20 | 141 | 45 (31) | 45 (30) | 0 (-3, 2) | Ref |
| Black |  |  |  |  |  |
| < 20 | 42 | 63 (32) | 53 (26) | -10 (-15, -5) | -8 (-13, -3) |
| > 20 | 117 | 51 (26) | 49 (26) | -2 (-5, 0) | Ref |
| Hispanic |  |  |  |  |  |
| < 20 | 12 | 59 (19) | 57 (16) | -2 (-9, 5) | -1 (-10, 8) |
| > 20 | 64 | 46 (21) | 45 (26) | -1 (-4, 3) | Ref |
| Chinese |  |  |  |  |  |
| < 20 | 8 | 44 (14) | 38 (14) | -7 (-15, 2) | -5 (-13, 3) |
| > 20 | 52 | 36 (18) | 34 (16) | -2 (-5, 1) | Ref |

25(OH)D, 25-hydroxyvitamin D.

aDifferences compare participants with baseline 25(OH)D < 20 ng/mL with those with 25(OH)D > 20 ng/mL. P = 0.134 for 25(OH)D category-race interaction).

**Supplemental Table 3. Associations of Baseline Characteristics with Change in Serum Total 1,25-Dihydroxyvitamin D Concentration (pg/mL) Among Participants Assigned to Vitamin D3**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  |  | **Unadjusted Model** | **Adjusted Model**a | |
| **Variable** | **N** | **Change in total 1,25(OH)2D from baseline, mean (95% CI)**b | **Difference in change in total 1,25(OH)2D (95% CI)**c | **Difference in change in total 1,25(OH)2D (95% CI)**c | **P-value** |
| Age (per decade) | 499 |  | 0 (-2, 2) | 0 (-2, 2) | 0.785 |
| Sex |  |  |  |  |  |
| Female | 272 | 2 (0, 4) | Ref | Ref | 0.412 |
| Male | 227 | 1 (-1, 3) | -1 (-4, 2) | -1 (-4, 2) |  |
| Race/ethnicity |  |  |  |  |  |
| White | 169 | 3 (0, 5) | Ref | Ref | 0.279 |
| Black | 184 | 3 (0, 5) | 0 (-3, 4) | 0 (-3, 4) |  |
| Hispanic | 82 | 1 (-3, 5) | -1 (-6, 3) | -2 (-6, 3) |  |
| Chinese | 64 | -2 (-6, 2) | -4 (-9, 0) | -5 (-10, 0) |  |
| BMI (kg/m2) |  |  |  |  |  |
| < 25 | 127 | 1 (-2, 4) | Ref | Ref | 0.876 |
| 25 - <30 | 189 | 1 (-1, 4) | 0 (-3, 4) | 0 (-4, 3) |  |
| 30 - <35 | 107 | 2 (-1, 5) | 1 (-3, 5) | 0 (-4, 5) |  |
| > 35 | 76 | 4 (0, 7) | 3 (-2, 7) | 1 (-4, 7) |  |
| eGFR (per 10 mL/min/1.73m2) | 499 |  | 0 (-1, 1) | 0 (-1, 1) | 0.817 |
| Bioavailable 25(OH)D (per 1 ng/mL decrement) | 499 |  | 0 (-1, 1) | 0 (-1, 1) | 0.714 |
| 25(OH)D (ng/mL) |  |  |  |  |  |
| < 20 | 79 | 3 (-1, 7) | 2 (-3, 6) | 2 (-3, 6) |  |
| 20 – <30 | 144 | 2 (-1, 4) | 0 (-3, 3) | 0 (-3, 4) |  |
| > 30 | 230 | 1 (-1, 4) | Ref | Ref | 0.731 |
| Per 10 ng/mL decrement | 499 |  | 0 (-1, 2) | 1 (-1, 2) | 0.441 |
| VDBP (per 1 SD increment) | 499 |  | 1 (-1, 2) | 1 (0, 3) | 0.117 |
| VDMR tertilesd |  |  |  |  |  |
| Tertile 1 | 149 | 3 (0, 5) | 0 (-3, 4) | 0 (-4, 4) |  |
| Tertile 2 | 155 | 0 (-2, 3) | -3 (-6, 1) | -2 (-6, 1) |  |
| Tertile 3 | 149 | 3 (0, 5) | Ref | Ref | 0.323 |
| Per 1 SD decrement | 499 |  | 0 (-1, 2) | 0 (-1, 2) | 0.664 |

1,25(OH)2D, 1,25-dihydroxyvitamin D; BMI, body mass index; eGFR, estimated glomerular filtration rate; 25(OH)D, 25-hydroxyvitamin D; VDBP, vitamin D binding protein; VDMR, vitamin D metabolite ratio (24,25-dihydroxyvitamin D3 to 25(OH)D3).

aAdjusted for age, sex, race/ethnicity, BMI, eGFR and season at baseline exam.  
bChange from baseline after 16 weeks of vitamin D3 summarized over all participants (N = 499) using multiple imputation. The mean (95% CI) among all vitamin D3 participants was 2 (0, 3) pg/mL.cModeled estimates account for missing data using multiple imputation.  
dTertile cut points are based on the entire study population.

**Supplemental Table 4. Associations of Baseline Characteristics with Change in Serum Total 25-Hydroxyvitamin D Concentration (ng/mL) Among Participants Assigned to Vitamin D3**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  |  | **Unadjusted Model** | **Adjusted Model**a | |
| **Variable** | **N** | **Change in total 25(OH)D from baseline, mean (95% CI)**b | **Difference in change in total 25(OH)D (95% CI)**c | **Difference in change in total 25(OH)D (95% CI)**c | **P-value** |
| Age (per decade) | 499 |  | 1 (0, 2) | 0 (-1, 2) | 0.740 |
| Sex |  |  |  |  |  |
| Female | 272 | 11 (9, 12) | Ref | Ref | 0.773 |
| Male | 227 | 10 (9, 12) | 0 (-2, 1) | 0 (-1, 2) |  |
| Race/ethnicity |  |  |  |  |  |
| White | 169 | 11 (9, 13) | Ref | Ref | 0.238 |
| Black | 184 | 11 (10, 13) | 1 (-2, 3) | 1 (-1, 3) |  |
| Hispanic | 82 | 9 (7, 10) | -2 (-4, 1) | -2 (-4, 1) |  |
| Chinese | 64 | 11 (9, 13) | 0 (-3, 3) | 0 (-3, 3) |  |
| BMI (kg/m2) |  |  |  |  |  |
| < 25 | 127 | 12 (10, 13) | Ref | Ref | 0.513 |
| 25 - <30 | 189 | 10 (9, 12) | -1 (-4, 1) | -1 (-4, 1) |  |
| 30 - <35 | 107 | 11 (9, 13) | -1 (-3, 2) | -1 (-4, 2) |  |
| > 35 | 76 | 9 (8, 11) | -2 (-5, 1) | -2 (-6, 1) |  |
| eGFR (per 10 mL/min/1.73m2) | 499 |  | 0 (-1, 0) | -1 (-1, 0) | 0.095 |
| Bioavailable 25(OH)D (per 1 ng/mL decrement) | 499 |  | 3 (3, 4) | 4 (3, 4) | <0.001 |
| 25(OH)D (ng/mL) |  |  |  |  |  |
| < 20 | 79 | 17 (15, 19) | 10 (7, 12) | 11 (9, 14) | <0.001 |
| 20 – <30 | 144 | 12 (10, 14) | 4 (2, 6) | 6 (4, 7) |  |
| > 30 | 230 | 8 (7, 9) | Ref | Ref |  |
| Per 10 ng/mL decrement | 499 |  | 4 (3, 4) | 4 (4, 5) | <0.001 |
| VDBP (per 1 SD increment) | 499 |  | 0 (-1, 1) | 0 (-1, 1) | 0.371 |
| VDMR tertilesd |  |  |  |  |  |
| Tertile 1 | 149 | 14 (13, 15) | 6 (4, 8) | 7 (5, 9) |  |
| Tertile 2 | 155 | 10 (9, 11) | 2 (0, 4) | 2 (0, 5) |  |
| Tertile 3 | 149 | 8 (6, 10) | Ref | Ref | <0.001 |
| Per 1 SD decrement | 499 |  | 3 (2, 4) | 3 (2, 4) | <0.001 |

BMI, body mass index; eGFR, estimated glomerular filtration rate; 25(OH)D, 25-hydroxyvitamin D; VDBP, vitamin D binding protein; VDMR, vitamin D metabolite ratio (24,25-dihydroxyvitamin D3 to 25(OH)D3).

aAdjusted for age, sex, race/ethnicity, BMI, eGFR and season at baseline exam.  
bChange from baseline after 16 weeks of vitamin D3 summarized over all participants (N = 499) using multiple imputation. The mean (95% CI) among all vitamin D3 participants was 11 (10, 11) ng/mL.cModeled estimates account for missing data using multiple imputation.  
dTertile cut points are based on the entire study population.

**Supplemental Table 5. Associations of Baseline Characteristics with Change in Urine Calcium Excretion Among Participants Assigned to Vitamin D3**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  |  | **Unadjusted Model** | **Adjusted Model\*** | |
| **Variable** | **N** | **Change in urine calcium excretion from baseline, mean (95% CI)**b | **Difference in change in urine calcium excretion (95% CI)**c | **Difference in change in urine calcium excretion (95% CI)**c | **P-value** |
| Age (per decade) | 499 |  | 5 (-4, 15) | 5 (-6, 17) | 0.338 |
| Sex |  |  |  |  |  |
| Female | 272 | 13 (2, 24) | Ref | Ref |  |
| Male | 227 | 3 (-5, 11) | -10 (-25, 5) | -10 (-25, 5) | 0.197 |
| Race/ethnicity |  |  |  |  |  |
| White | 169 | 10 (-4, 24) | Ref | Ref | 0.974 |
| Black | 184 | 8 (-2, 17) | -2 (-20, 16) | -1 (-19, 17) |  |
| Hispanic | 82 | 10 (-5, 24) | 0 (-22, 22) | -1 (-23, 22) |  |
| Chinese | 64 | 6 (-20, 32) | -4 (-28, 20) | -6 (-31, 19) |  |
| BMI (kg/m2) |  |  |  |  |  |
| < 25 | 127 | 13 (-2, 28) | Ref | Ref | 0.648 |
| 25 - <30 | 189 | 11 (-3, 24) | -3 (-22, 16) | -3 (-23, 17) |  |
| 30 - <35 | 107 | 7 (-4, 18) | -7 (-28, 15) | -7 (-30, 16) |  |
| > 35 | 76 | -2 (-15, 11) | -15 (-40, 9) | -16 (-43, 11) |  |
| eGFR (per 10 mL/min/1.73m2) | 499 |  | 0 (-5, 4) | 1 (-4, 6) | 0.687 |
| Bioavailable 25(OH)D (per 1 ng/mL decrement) | 499 |  | 3 (-3, 9) | 4 (-2, 10) | 0.186 |
| 25(OH)D (ng/mL) |  |  |  |  |  |
| < 20 | 79 | 8 (-4, 21) | 3 (-19, 24) | 8 (-14, 31) |  |
| 20 – <30 | 144 | 13 (0, 26) | 8 (-9, 24) | 10 (-7, 28) |  |
| > 30 | 230 | 6 (-6, 17) | Ref | Ref | 0.483 |
| Per 10 ng/mL decrement | 499 |  | 2 (-5, 9) | 4 (-3, 12) | 0.282 |
| VDBP (per 1 SD increment) | 499 |  | -5 (-12, 3) | -4 (-12, 4) | 0.345 |
| VDMR tertilesd |  |  |  |  |  |
| Tertile 1 | 149 | 12 (1, 24) | 5 (-12, 24) | 9 (-11, 28) | 0.661 |
| Tertile 2 | 155 | 6 (-8, 20) | 0 (-19, 18) | 2 (-17, 22) |  |
| Tertile 3 | 149 | 7 (-7, 20) | Ref | Ref |  |
| Per 1 SD decrement | 499 |  | 0 (-7, 8) | 1 (-6, 9) | 0.721 |

BMI, body mass index; eGFR, estimated glomerular filtration rate; 25(OH)D, 25-hydroxyvitamin D; VDBP, vitamin D binding protein; VDMR, vitamin D metabolite ratio (24,25-dihydroxyvitamin D3 to 25(OH)D3).

aAdjusted for age, sex, race/ethnicity, BMI, eGFR and season at baseline exam.  
bChange in spot urine calcium to creatinine ratio (mg/g) from baseline after 16 weeks of vitamin D3 summarized over all participants (N = 499) using multiple imputation. The mean (95% CI) among all vitamin D3 participants was 9 (1, 16) mg/g.cModeled estimates account for missing data using multiple imputation.  
dTertile cut points are based on the entire study population.

**Supplemental Table 6. Adverse Events**

|  |  |  |
| --- | --- | --- |
| **Outcome by Organ System** | **Placebo**  **(N = 167), N (%)** | **Vitamin D3**  **(N = 499), N (%)** |
| Cardiac disorders | 1 (1) | 5 (1) |
| Gastrointestinal disorders | 6 (4) | 22 (4) |
| General disorders and administration site conditions | 1 (1) | 8 (2) |
| Immune system disorders | 2 (1) | 8 (2) |
| Metabolism and nutrition disorders | 1 (1) | 2 (<1) |
| Musculoskeletal, connective tissue and bone disorders | 2 (1) | 5 (1) |
| Neoplasms benign, malignant and unspecified | 0 (0) | 1 (<1) |
| Psychiatric disorders | 1 (1) | 0 (0) |
| Renal and urinary tract disorders | 2 (1) | 1 (<1) |
| Respiratory, thoracic and mediastinal disorders | 0 (0) | 2 (<1) |
| Unknown | 0 (0) | 1 (<1) |

**Supplemental Figure 1. Participants Flow in the Multi-Ethnic Study of Atherosclerosis Individualized Response to Vitamin D Treatment Trial**

